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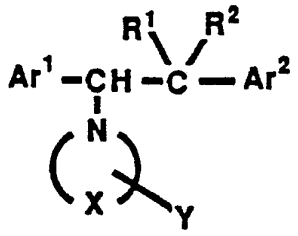
(54) 1,2-diarylethylamines for treatment of neurotoxic injury.

(57) Compounds, compositions and methods of treatment are described to control brain damage associated with anoxia or ischemia which typically follows stroke, cardiac arrest or perinatal asphyxia. The treatment includes administration of a 1,2-diarylethylamine compound as an antagonist to inhibit excitotoxic actions at major neuronal excitatory amino acid receptor sites. Compounds of interest are those of the formula



wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, hydroxyl, alkoxy, halo, cyano, nitro and mercapto, or wherein R^1 and R^2 may be taken together to form an oxo group or to form a saturated or partially unsaturated carbocyclic group having three to eight ring carbons; wherein each of Ar^1 and Ar^2 is a group independently selected from aryl and heteroaryl having one or two heteroatoms selected from N, O and S; and wherein any of the foregoing Ar^1 and Ar^2 groups having a substitutable position msy be substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, alkenyl, alkynyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein X is selected from CH, CH_2, NH, O and S, to form a ring having five to eight members provided that such ring is saturated or contains one double bond or is benzo-fused; and wherein Y is one or more a groups selected from hydrido, alkyl, cycloalkyl, halo,

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haloalkyl, alkenyl, alkynyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; or a pharmaceutically acceptable salt thereof.

1,2-DIARYLETHYLAMINES FOR TREATMENT OF NEUROTOXIC INJURY

FIELD OF THE INVENTION

This invention is in the field of clinical neurology and relates specifically to compounds, compositions and methods for neuroprotective purposes such as controlling brain damage which occurs during periods of anoxia or ischemia associated with stroke, cardiac arrest or perinatal asphyxia.

BACKGROUND OF THE INVENTION

Unlike other tissue which can survive extended periods of hypoxia, brain tissue is particularly sensitive to deprivation of oxygen or energy. Permanent damage to neurons can occur during brief periods of hypoxia, anoxia or ischemia. Neurotoxic injury is known to be caused or accelerated by certain excitatory amino acids (EAA) found naturally in the central nervous system (CNS). Glutamate (Glu) is an endogenous amino acid which was early characterized as a fast excitatory transmitter in the mammalian brain. Glutamate is also known as a powerful neurotoxin capable of killing CNS neurons under certain pathological conditions which accompany stroke and cardiac arrest. Normal glutamate concentrations are maintained within brain tissue by energy-consuming transport systems. Under low energy conditions which occur during periods of hypoglycemia, hypoxia or ischemia, cells can release glutamate. Under such low energy conditions the cell is not able to take glutamate back into the cell. Initial glutamate release stimulates further release of glutamate which results in an extracellular glutamate accumulation and a cascade of neurotoxic injury.

It has been shown that the sensitivity of central neurons to hypoxia and ischemia can be reduced by either interfering with synaptic transmission through blockade of the sodium or calcium ion channel or by the specific antagonism of postsynaptic glutamate receptors [see S. M. Rothman and J. W. Olney, "Glutamate and the Pathophysiology of Hypoxia -Ischemic Brain Damage," Annals of Neurology, Vol. 19, No. 2 (1986)]. Glutamate is characterized as a broad spectrum agonist having activity at three neuronal excitatory amino acid receptor sites. These receptor sites are named after the amino acids which selectively excite them, namely: kainate (KA), N-methyl-D-aspartate (NMDA or NMA) and quisqualate (QUIS). Glutamate is believed to be a mixed agonist capable of binding to and exciting all three receptor types.

Neurons which have EAA receptors on their dendritic or somal surfaces undergo acute excitotoxic degeneration when these receptors are excessively activated by glutamate. Thus, agents which selectively block or antagonize the action of glutamate at the EAA synaptic receptors of central neurons can prevent neurotoxic injury associated with anoxia, hypoxia or ischemia caused by stroke, cardiac arrest or perinatal asphyxia.

Phencyclidine (PCP) and the PCP-like compound ketamine have been found to reduce selectively the excitatory effects of NMDA as compared to KA and QUIS [Anis, N.A. et al, "The Dissociative Anaesthetics, Ketamine and Phencyclidine, Selectively Reduce Excitation of Central Mammalian Neurones by N-Methyl-Aspartate", Br. J. Pharmacol., 79, 565 (1983)]. Other compounds having PCP-like properties such as cyclazocine, kynurenate and various barbiturates such as secobarbital, amobarbital and pentobarbital, have been tested as antagonists in blocking NMDA- or KA-induced neurotoxicity [J. W. Olney et al., "The Anti-Excitotoxic Effects of Certain Anesthetics, Analgesics and Sedative-Hypnotics," Neuroscience Letters, 68, 29-34 (1986)].

A correlation has been found between the PCP binding effects of some PCP-derivative stereoisomers and NMDA antagonism. For example, the stereoselective effects of cis-N-(1-phenyl-4-methylcyclohexyl)-piperidine and (+)-1-(1-phenylcyclohexyl)-3-methylpiperidine [(+)-PCMP] over each of their corresponding isomer counterparts in reducing the excitatory action of NMDA have been confirmed in binding and behavioral data [S.D. Berry et al, "Stereoselective Effects of Two Phencyclidine Derivatives on N-Methylaspartate Excitation of Spinal Neurones in the Cat and Rat", Eur. J. Pharm., 96, 261-267 (1983)]. Also, the compound (+)-PCMP has been found to be a potent inhibitor of the specific binding of [^{3}H]PCP to rat cerebral cortical membranes [M. E. Goldman et al, "Differentiation of [^{3}H]Phencyclidine and (+)-[^{3}H]-SKF-10,047 Binding Sites in Rat Cerebral Cortex", FEBS Lett., 170, 333-336 (1985)].

Other neurochemical mechanisms by which PCP alters behavior are known. For example, binding assays of the PCP/sigma site have been used to evaluate arylcycloalkylamines [R. Quirion, "Phencyclidine (Angel Dust)/Sigma 'Opiate' Receptor: Visualization by Tritium-Sensitive Film", Proc. Natl. Acad. Sci. U.S.A.,

78, 5881 (1981)]. PCP-like drugs may induce ipsilateral turning in rats by action on the PCP/sigma receptor as indicated by studies with arylcycloalkylamines, sigma-agonist benzomorphans and 1,3-dioxolanes.

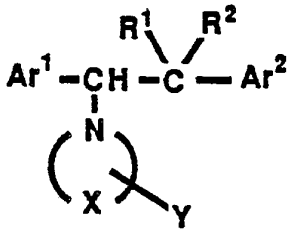
These PCP-like classes of compounds have been found to inhibit NMDA-induced acetylcholine (ACh) release and such ACh release has been correlated with their affinity for the PCP receptor and with behavioral activity [L. D. Snell et al, "Antagonism of N-Methyl-D-Aspartate-Induced Transmitter Release in the Rat Striatum by Phencyclidine-Like Drugs and its Relationship to Turning Behavior", J. Pharmacol.Exp. Ther., 235, No. 1, 50-56 (1985)].

Certain 1,2-diarylethylamines have been described for use as human pharmaceutical therapeutic purposes. For example, U.K. Patent No. 1,143,263 mentions (±)-1,2-diphenyl-2-(1-piperidinyl)ethanone for use as an anti-depressant. Japanese Patent No. 8526/61 mentions (±)-1-(1,2-diphenylethyl)piperidine as having actions on the central nervous system and mentions several possible uses for the compound, namely as an anti-tussive, as an anesthetic or as a monoamine oxidase inhibitor. Japanese Patent No. 15,937 mentions (±)-1-[2-phenyl-1-(2-thienyl)ethyl]piperidine hydrosulfate for use as an anti-spasmodic, analgesic or an anti-tussive. The compound (±)-1-(1,2-diphenylethyl)pyrrolidine has been mentioned for sympathomimetic or bronchodilator uses [R.V. Heinzelmann et al, J. Am. Chem. Soc., 75 3409-3413 (1953)-].

Other 1,2-diarylethylamines have also been described without mention of pharmaceutical utility. For example, the compound (±)-1-(1,2-diphenyl-1-hydroxyethyl)piperidine is mentioned as an intermediate to making certain derivatives of the alkaloid bicuculline which is a convulsant [T.V. Hung et al, Aust. J. Chem., 34, 383-395 (1981)]. The laboratory synthesis of the compounds (±)-1-[1-(4-methylphenyl)-2-phenylethyl]-piperidine and (±)-1-[1-(4-methoxyphenyl)-2-phenylethyl)piperidine has been described without mention of any pharmaceutically-related use [L.A. Goodson et al, J. Am. Chem. Soc., 72, 358-362 (1950)].

DESCRIPTION OF THE INVENTION

Control of neuropathological processes and the neurodegenerative consequences thereof in mammals is provided by treating a mammal susceptible to neurotoxic injury with an anti-excitotoxic amount of a compound of a class of 1,2-diarylethylamines represented by formula I:



(I)

wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, hydroxyl, alkoxy, halo, cyano, nitro and mercapto, or wherein R^1 and R^2 may be taken together to form an oxo group or to form a saturated or partially unsaturated carbocyclic group having three to eight ring carbons; wherein each of Ar^1 and Ar^2 is a group independently selected from aryl and heteroaryl having one or two heteroatoms selected from N, O and S; and wherein any of the foregoing Ar^1 and Ar^2 groups having a substitutable position may be substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, alkenyl, alkynyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein X is selected from CH, CH_2, NH, O and S, to form a ring having five to eight members provided that such ring is saturated or contains one double bond or is benzo-fused; and wherein Y is one or more a groups selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, alkenyl, alkynyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; or a pharmaceutically acceptable salt thereof.

A preferred class of compounds within formula I consists of those compounds wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl, cycloalkyl, hydroxyl, halo and alkoxy, or wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to eight ring carbons; wherein each of Ar^1 and Ar^2 is independently selected from phenyl, thienyl, furanyl, pyridinyl, thiazolyl and naphthyl groups, and wherein any of the foregoing Ar^1 and Ar^2 groups having a substitutable position may be substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl,

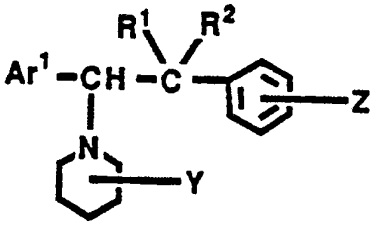
halo, haloalkyl, alkenyl, alkynyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein X is selected from CH, CH_2, NH, O and S, to form a ring having five to eight members provided that such ring is saturated or contains one double bond; and wherein Y is a group selected from hydrido, alkyl, halo, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto.

A more preferred class of compounds within Formula I consists of those compounds wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl, cycloalkyl, hydroxyl, halo and alkoxy, or wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated cycloalkyl carbocyclic group having three to eight ring carbons; wherein each of Ar^1 and Ar^2 is a group independently selected from phenyl, thienyl, furanyl, pyridinyl, thiazolyl and naphthyl groups, and wherein any of the foregoing Ar^1 and Ar^2 groups may be substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, alkenyl, alkynyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein X is selected from CH or CH_2 to form a ring having five to seven members provided that such ring is saturated or contains one double bond; and wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy, amino, cyano, nitro and mercapto.

It is believed that the compounds defined by Formula I are novel where the Formula I definition is qualified by the following proviso descriptions:
when each of Ar^1 and Ar^2 is phenyl and each of R^1 and R^2 is hydrido or R^1 and R^2 together form oxo, then X cannot be a linear alkylene chain having four or five carbon atoms so as to form a racemic mixture;
when Ar^1 is thiophene, then X cannot be oxygen atom or a linear alkylene chain having five carbon atoms; and
when Ar^1 is para-methylphenyl or para-methoxyphenyl, each of R^1 and R^2 is hydrido and Ar^2 is phenyl, then X cannot be a linear alkylene chain having five carbon atoms.

With regard to the foregoing proviso descriptions, it is intended that where specific substituents are recited, such proviso relates to those specific substituents, only, and not to substituents modified by removal or addition of a radical. For example, where Ar^1 or Ar^2 is phenyl or thiophene, then such proviso does not exclude substituted phenyl or substituted thiophene unless otherwise specified. Also, it is intended that where a racemate is excluded from Formula I by a proviso description, individual isomers of such racemate remain within the scope of Formula I.

A more particularly preferred class of compounds within Formula I contains a first sub-class of compounds defined by Formula II:



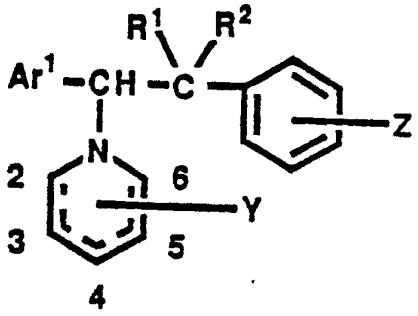
(II)

wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl, cycloalkyl, hydroxyl, halo and alkoxy, or wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to seven ring carbons; wherein Ar^1 is a group selected from phenyl, thienyl, furanyl, pyridinyl, thiazolyl and naphthyl groups, and wherein any of the foregoing Ar^1 groups having a substitutable position may be substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy and amino; and wherein Z is one or more groups selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto.

A more highly preferred class of compounds within the first sub-class of compounds of Formula II consists of those compounds wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl, cycloalkyl, hydroxyl, halo and alkoxy, or wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to seven ring carbons; wherein Ar^1 is selected from phenyl, thienyl, pyridinyl and naphthyl groups, and wherein any of the foregoing Ar^1 groups having a substitutable position may be substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy and amino; and wherein Z is one or more groups selected from hydrido, alkyl, cycloalkyl, halo, hydroxyl, alkoxy and amino.

A most preferred class of compounds within the first sub-class of compounds of Formula II consists of those compounds wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl and hydroxyl, or wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to six ring carbons; wherein Ar^1 is a group selected from phenyl, thienyl, pyridinyl and naphthyl groups, and wherein any of the foregoing Ar^1 groups having one or more substitutable position may be substituted with one or more radicals selected from hydrido, alkyl, halo, haloalkyl, hydroxyl, alkoxy, amino and nitro; wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy and amino; and wherein Z is one or more groups selected from hydrido, alkyl, halo, hydroxyl and alkoxy.

A second sub-class of more particularly preferred compounds within Formula I contains a first sub-class of compounds defined by of Formula III:



(III)

wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl, cycloalkyl, hydroxyl, halo and alkoxy, or wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to seven ring carbons; wherein Ar^1 is a group selected from phenyl, thienyl, furanyl, pyridinyl, thiazolyl and naphthyl groups, and wherein any of the foregoing Ar^1 groups having a substitutable position is substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy and amino; wherein Z is one or more groups selected from alkyl, cycloalkyl, halo, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; and wherein the broken line within the N-containing ring represents a double bond between any two adjacent carbon atoms involving the 2-, 3-, 4-, 5-and 6-positions of the N-containing ring.

A more highly preferred class of compounds within the second sub-class of compounds of Formula III consists of those compounds wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl, cycloalkyl, hydroxyl, halo and alkoxy, or wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to seven ring carbons; wherein Ar^1 is a group selected from phenyl, thienyl, furanyl, pyridinyl, thiazolyl and naphthyl groups, and wherein any of the foregoing groups having one or more substitutable positions may be substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy and amino; wherein Z is one or more groups selected from hydrido, alkyl, cycloalkyl, halo, hydroxyl, alkoxy and amino; and wherein the broken line within the N-containing ring represents a double bond between any two adjacent carbon atoms involving the 3-, 4-, 5-positions of the N-containing ring.

An even more highly preferred class of compounds within the second sub-class of compounds of Formula III consists of those compounds wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl, cycloalkyl, hydroxyl, halo and alkoxy; wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated cycloalkyl having three to seven ring carbons; wherein Ar^1 is selected from phenyl, thienyl, pyridinyl and naphthyl groups, and wherein any of the foregoing groups having a substitutable position is substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, hydroxyl, hydroxylalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy and amino; wherein Z is one or more groups selected from hydrido, alkyl, cycloalkyl, halo, hydroxyl, alkoxy and amino; and wherein the broken line within the N-containing ring represents either a double bond between any two adjacent carbon atoms involving the 3-, 4-, 5-positions of the N-containing ring.

A most preferred class of compounds within the second sub-class of compounds of Formula III consists of those compounds wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl and

hydroxyl; wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated cycloalkyl having three to six ring carbons; wherein Ar^1 is selected from phenyl, thienyl, pyridinyl and naphthyl groups, and wherein any of the foregoing groups having one or more substitutable positions is substituted with one or more radicals selected from hydrido, alkyl, halo, haloalkyl, hydroxyl, alkoxy, amino and nitro; wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy and amino; wherein Z is one or more groups selected from hydrido, alkyl, halo, hydroxyl and alkoxy; and wherein the broken line within the N-containing ring represents either a double bond between any two adjacent carbon atoms involving the 3-, 4-, 5-positions of the N-containing ring.

Specific compounds of Formula II which are most highly preferred compounds are the following:

(-)-1-(1,2-diphenylethyl)piperidine;
(+)-1-(1,2-diphenylethyl)piperidine;
1-(1,2-diphenylethenyl)piperidine;
(±)-1-[1-phenyl-2-(2-pyridinyl)ethyl]piperidine;
1-[1-phenyl-2-(2-pyridinyl)ethenyl]piperidine;
(±)-1-(1,2-diphenylethyl)-1H-azepine;
(±)-1-(1,2-diphenylbutyl)piperidine;
(±)-1-(1,2-diphenyl-3-methylbutyl)piperidine;
(±)-1-(1,2-diphenylethyl)-4-methylpiperazine;
(±)-1-(1,2-diphenylethyl)morpholine;
(±)-1-[1-(1-phenylcyclopentyl)benzyl]piperidine;
(±)-1-[1,2-di(4-methoxyphenyl)ethyl]piperidine;
(±)-1-[1-(1-phenylcyclohexyl)benzyl]piperidine;
(±)-1-[1-(1-phenylcyclopropyl)benzyl]piperidine;
(±)-1-(1,2-diphenylethyl)-3,5-dimethylpiperidine;
(±)-1-[2,2-dimethyl-2-phenyl-1-(2-thienyl)ethyl]piperidine;
(±)-1-[1-(3-methoxyphenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(4-fluorophenyl)-2-phenylethyl]piperidine;
(±)-1-(2,2-dimethyl-1,2-diphenylethyl)piperidine;
(±)-1-[1-(3-methylphenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(2-furyl)-2-phenylethyl]piperidine;
(±)-1-[1-(2-chlorophenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(2-methoxyphenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(1-naphthyl)-2-phenylethyl]piperidine.

Specific compounds of Formula III which are most highly preferred compounds are the following: (±)-1-(1,2-diphenylethyl)-1,2,3,6-tetrahydropyridine and (±)-1-[2-phenyl-1-(2-thienyl)ethyl]-1,2,3,6-tetrahydropyridine.

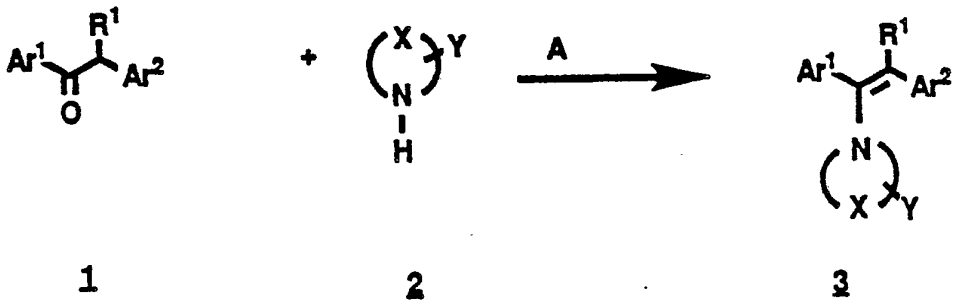
The term "hydrido" denotes a single hydrogen atom (H) which may be attached, for example, to a carbon atom or attached to an oxygen atom to form an hydroxyl group. Where the term "alkyl" is used, either alone or within other terms such as "haloalkyl" and "hydroxyalkyl", the term "alkyl" embraces linear or branched radicals having one to about twenty carbon atoms or, preferably, one to about ten carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about five carbon atoms. The term "cycloalkyl" embraces cyclic radicals having three to about ten ring carbon atoms, preferably three to about six carbon atoms, such as cyclopropyl and cyclobutyl. The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with one or more halo groups, preferably selected from bromo, chloro and fluoro. Specifically embraced by the term "haloalkyl" are monohaloalkyl, dihaloalkyl and polyhaloalkyl groups. A monohaloalkyl group, for example, may have either a bromo, a chloro, or a fluoro atom within the group. Dihaloalkyl and polyhaloalkyl groups may be substituted with two or more of the same halo groups, or may have a combination of different halo groups. A dihaloalkyl group, for example, may have two bromo atoms, such as a dibromomethyl group, or two chloro atoms, such as a dichloromethyl group, or one bromo atom and one chloro atom, such as a bromochloromethyl group. Examples of a polyhaloalkyl are trifluoromethyl, 2,2,2-trifluoroethyl, perfluoroethyl and 2,2,3,3-tetrafluoropropyl groups. The terms "alkylol" and "hydroxyalkyl" embrace linear or branched alkyl groups having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl groups. The term "alkenyl" embraces linear or branched radicals having two to about twenty carbon atoms, preferably three to about ten carbon atoms, and containing at least one carbon-carbon double bond. The term "alkynyl" embraces linear or branched radicals having two to about twenty carbon atoms, preferably two to about ten carbon atoms, and containing at least one carbon-carbon triple bond. The terms "cycloalkenyl" and "cycloalkynyl" embrace cyclic radicals having three to about ten ring carbon atoms

including, respectively, one or more double or triple bonds involving adjacent ring carbons. The terms "alkoxy" and "alkoxyalkyl" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms, such as methoxy group. The "alkoxy" or "alkoxyalkyl" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide haloalkoxy or haloalkoxyalkyl groups. The term "heteroaryl" embraces aromatic ring systems containing one or two hetero atoms selected from oxygen, nitrogen and sulfur in a ring system having five or six ring members, examples of which are thienyl, furanyl, pyridinyl, thiazolyl, pyrimidyl and isoxazolyl. The term "alkylene chain" describes a chain of two to six methylene ($-CH_2-$) groups which, as shown in Formula I, may form a cyclic structure including the nitrogen atom of Formula I.

Specific examples of alkyl groups are methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, iso-pentyl, methylbutyl, dimethylbutyl and neopentyl. Typical alkenyl and alkynyl groups may have one unsaturated bond, such as an allyl group, or may have a plurality or unsaturated bonds, with such plurality of bonds either adjacent, such as allene-type structures, or in conjugation, or separated by several saturated carbons.

Included within the family of compounds of Formulas I-III are the tautomeric forms of the described compounds, isomeric forms including diastereoisomers, and the pharmaceutically-acceptable salts thereof. The term "pharmaceutically-acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. Since the compounds of Formulas I-III contain basic nitrogen atoms, such salts are typically acid addition salts or quaternary salts. The nature of the salt is not critical, provided that it is pharmaceutically acceptable, and acids which may be employed to form such salts are, of course, well known to those skilled in this art. Examples of acids which may be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, sulfuric acid and phosphoric acid, and such organic acids as maleic acid, succinic acid and citric acid. Other pharmaceutically acceptable salts include salts with alkali metals or alkaline earth metals, such as sodium, potassium, calcium and magnesium, or with organic bases, such as dicyclohexylamine. All of these salts may be prepared by conventional means by reacting, for example, the appropriate acid or base with the corresponding compound of Formulas I-III.

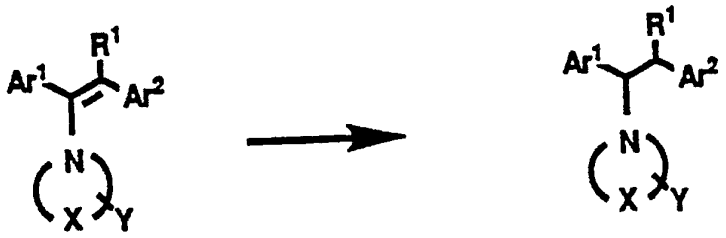
Compounds of Formulas I-III may be prepared in accordance with the following general procedures:



1 2 3

wherein Ar^1, Ar^2, R^1, X and Y are as defined before; wherein A can be a variety of Bronsted or Lewis acids such as p-toluenesulfonic acid, hydrochloric acid, sulfuric acid, titanium tetrachloride, stannous chloride, or zinc chloride.

One of the processes that can be used to synthesize the products of the invention starts with diarylketones of general formula 1 where R^1, Ar^1 and Ar^2 have the values defined previously, and with a cyclic secondary amine of general formula 2 where X and Y have the values defined previously. The ketone is treated with the amine in the presence of a variety of Bronsted or Lewis acids like p-toluenesulfonic acid, hydrochloric acid, sulfuric acid, titanium tetrachloride, stannous chloride, or zinc chloride to generate the imine of general formula 3. The reaction is best achieved by mixing the reagents in a solvent like toluene, ethyl acetate or lower alkane like hexane or heptane, and the reaction temperature can vary from about 0 °C to reflux of the reaction mixture.

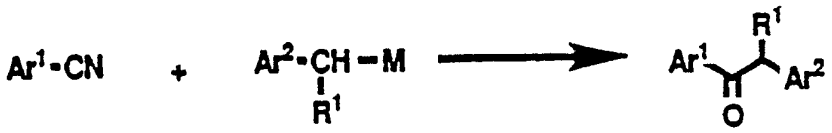


3 4

wherein Ar^1, Ar^2, R^1 X, and Y are as defined before.

In the second step of the process, the imine 3 is transformed into the amine 4 by reduction in a protic or aprotic solvent. Possible reducing agents to perform this transformation are lithium aluminum hydride, sodium borohydride, sodium cyanoborohydride, borane, or any other reducing systems familiar to those skilled in the art.

The reagent ketones of general formula 1 can be prepared in accordance with the following generic procedure:

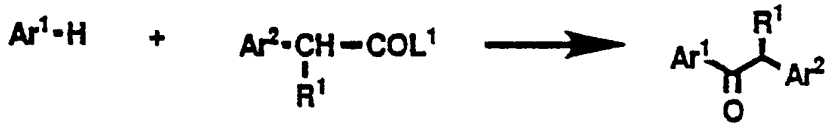


5 6 1

wherein Ar^1, Ar^2, R^1 are as defined before; M = Li, MgBr, MgCl, CuCl, or CuBr.

One of the processes that can be used to generate the ketones of general formula 1 starts with nitriles of general formula 5 where Ar^1 is as defined previously. This nitrile is treated with an organo-metallic reagent of general formula 6 where Ar^2 and R^1 are as defined previously and M represents a metal or metal complex such as Li, MgCl, MgBr, CuCl, or CuBr. This reaction is best achieved by mixing the reagents in a solvent like toluene, tetrahydrofuran, ether, or dioxane, and the reaction temperature can vary from 0 °C to reflux of the reaction mixture. The reaction product is isolated under acidic conditions in the presence of water to obtain the ketone product.

Alternately, the ketone can be prepared according to the following generic procedure:

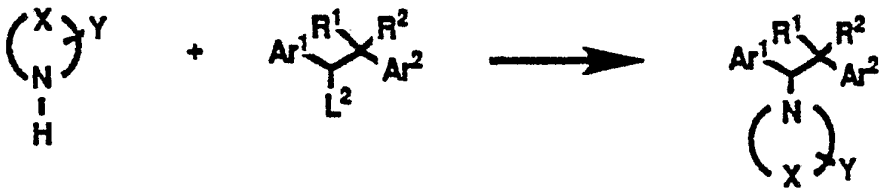


7 8 1

wherein Ar^1, Ar^2, and R^1 are as defined before. L^1 is selected from halogen, OH, or OR3; R3 = lower alkyl, aryl or benzyl.

The ketone of general formula 1 can alternately be prepared by mixing the arene of general formula 7 where Ar^1 is as previously described with the carboxylic acid derivative of general formula 8 where Ar^2 and R^1 are as defined before. L^1 is a good leaving group, which is , for example, halogen, OH, alkoxy, or aryloxy. The reaction is best achieved by mixing the reagents either neat or in a solvent like ether, tetrahydrofuran, dioxane or lower alkane such as hexane or heptane, in the presence of an appropriate catalyst B. If L^1 is OH, B is a dehydrating catalyst such as phosphorus oxychloride, phosphorus pentoxide, polyphosphoric acid or sulfuric acid. If L^1 is alkoxy or aryloxy, a strongly acidic catalyst such as sulfuric acid, phosphoric acid or hydrochloric acid may be used. When L^1 is halogen, Lewis acid catalysts such as aluminum chloride, ferric chloride, and zinc chloride are preferred. The reaction temperature can vary from 0 °C to reflux of the reaction mixture.

Generic Procedure II



2 9 10

wherein Ar^1, Ar^2, R^1, R^2 X, and Y are as defined previously. L^2 is halogen, tosylate, mesylate, brosylate, or OH.

The compounds of the invention may be prepared by displacement of the leaving group L^2 in general formula 9 by the appropriate secondary amine of general formula 2. Good leaving groups are, for example, halogen, tosylate, mesylate, and brosylate. The conversion can be best achieved by mixing the reagents either neat or in a solvent like acetonitrile, dimethylformamide, dimethylsulfoxide, or tetrahydrofuran, and the reaction temperature can vary from 0 ° C to 100 ° C.

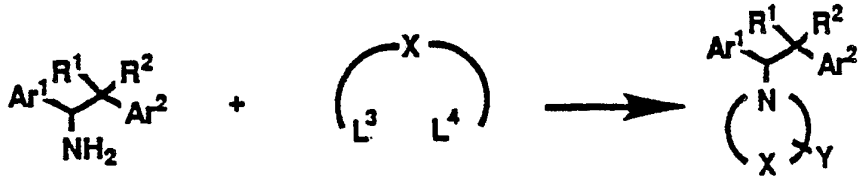
The reagents of general formula 9 can be prepared in accordance with the following generic procedure:

11 9

wherein Ar^1, Ar^2, R^1, R^2 and L^2 are as previously defined.

One of the processes that can be used to generate the compounds of general formula 9 is conversion of the oxo group in ketones of general formula 11 to a leaving group L^2, where L^2 is as previously defined. The oxo group can be reduced employing reagents such as lithium aluminum hydride, sodium borohydride, sodium cyanoborohydride, or other reducing agents familiar to those skilled in the art. This reduction can be accomplished in either protic or aprotic solvents, depending on the reducing agent of choice, and at temperatures ranging from 0 ° C to reflux of the reaction mixture. The resulting OH is then converted to a good leaving group, L^2, through functionalization by reagents such as p-tosyl chloride, brosyl chloride or mesyl chloride or by displacement with a halogen by reagents such as thionyl chloride, thionyl bromide, phosphorus oxychloride, or other reagents familiar to those skilled in the art.

Generic Procedure III



12 13 10

wherein each of L^3, L^4 is independently halogen, tosylate, brosylate, mesylate, OH; Ar^1, Ar^2, R^1, R^2, X, and Y are as previously described.

The products of the invention may be prepared by mixing the primary amine of general formula 12 with reagents of general formula 13 where X and Y have been defined previously and L^3 and L^4 represent good leaving groups. Good leaving groups are, for example, halogen, tosylate, brosylate, and mesylate. The reaction is best accomplished in a solvent like acetonitrile, dimethylformamide, dimethylsulfoxide, or tetrahydrofuran in the presence of a non-nuleophilic base such as sodium bicarbonate, potassium carbonate or other inorganic bases.

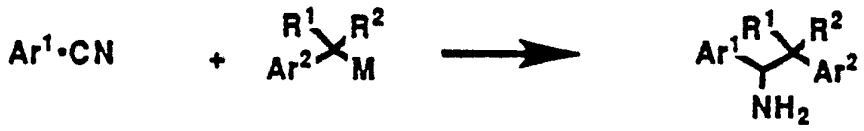
The primary amines of general formula 12 can be prepared according to the following generic procedure:

11 12

wherein Ar^1, Ar^2, R^1 and R^2 are previously defined.

One procedure for the preparation of the primary amines of general formula 12 is through the conversion of ketones of general formula 11. This conversion can be accomplished by the preparation of an oxime intermediate with hydroxylamine and reduction of the oxime with reagents such as lithium aluminum hydride, sodium borohydride, and other reagents familiar to those skilled in the art. The amine can also be prepared directly from the ketone by employing reductive amination procedures such as catalytic hydrogenation, sodium borohydride, sodium cyanoborohydride or other reducing conditions in the presence of ammonia or ammonium salts. The ketones of general formula 11 are prepared using the same generic procedures described previously for the preparation of ketones of general formula 1.

The amine 12 can also be prepared by the following generic procedure:



5 14 12

wherein Ar^1, Ar^2, R^1, R^2 and M have been previously defined.

Another process that can be used to generate the amines of general formula 12 starts with nitriles of general formula 5 where Ar^1 is as defined previously. This nitrile is treated with an organometallic reagent of general formula 14 where Ar^2 and R^1 are as defined previously and M represents a metal or metal complex such as Li, MgCl, MgBr, CuCl, or CuBr. This reaction is best achieved by mixing the reagents in a solvent like toluene, tetrahydrofuran, ether, or dioxane, and the reaction temperature can vary from 0 °C to reflux of the reaction mixture. The intermediate imine reaction product is isolated under anhydrous conditions and immediately reduced to the primary amine using reagents such as sodium borohydride, sodium cyanoborohydride, lithium aluminum hydride or hydrogen with appropriate catalysts, in a protic or aprotic solvent that is compatible with the reducing agent.

The following Examples I-XX are detailed descriptions of the methods of preparation of compounds of Formula I. These detailed preparations fall within the scope of, and serve to exemplify, the above described Generic Procedures which form part of the invention. These Examples I-XX are presented for illustrative purposes only and are not intended as a restriction on the scope of the invention. All parts are by weight unless otherwise indicated. Most of the commercially available starting materials were obtained from Aldrich Chemical Company, Milwaukee, Wisconsin.

Example I

2-(4-Methylphenyl)acetophenone

Benzylmagnesium chloride (21.4 ml, 2 M solution in tetrahydrofuran) was cooled to 0 ° C under argon. A solution of p-tolunitrile (5 gm) in anhydrous tetrahydrofuran (25 ml) was added dropwise to the Grignard reagent. After the addition, the mixture was heated to reflux and the heating continued for 20 hours. The reaction mixture was cooled in an ice bath and treated dropwise with cold 6 N hydrochloric acid (50 ml). The mixture was heated to reflux and the heating continued for 4 hours. The reaction mixture was allowed to cool to room temperature. The mixture was extracted with ether (3 X 75 ml) and methylene chloride (2 X 50 ml). The organic solutions were combined, dried over magnesium sulfate, and concentrated on a rotary evaporator to yield a yellow solid. The product was purified by distillation on a Kugelrohr apparatus (110-120 ° C @ 0.04 mm Hg) to yield a colorless oil which solidified upon standing.

Example II

1-[1-(4-Methylphenyl)-2-phenylethyl]piperidine

2-(4-Methylphenyl)acetophenone (3 gm) and p-toluenesulfonic acid (2.71 gm) were combined with toluene (50 ml). Piperidine (14.1 ml) was added all at once and the mixture heated to reflux. The heating was continued for 20 hours, with removal of the water that was generated during the condensation through use of a Dean-Stark trap. The reaction solution was allowed to cool to room temperature and diluted with ether (50 ml). The organic solution was washed with water (2 X 25 ml), dried over magnesium sulfate and concentrated on a rotary evaporator. The resulting yellow oil was dissolved in ethanol (75 ml) and treated all at once with glacial acetic acid (5 ml) and acetic anhydride (1 ml). Sodium cyanoborohydride (900 mg) was added to the solution and the mixture heated to reflux. The heating was continued for 20 hours. The solution was allowed to cool to room temperature and treated with water (75 ml), followed by enough ammonium hydroxide to make the solution basic. The resulting solution was extracted with ether (3 X 50 ml) and the combined ether extracts were extracted with cold 3.5 N sulfuric acid (3 X 30 ml). The combined acid solutions were made basic by the addition of 50% sodium hydroxide solution. The aqueous mixture was extracted with ether (3 X 50 ml), and the combined ether extracts dried over magnesium sulfate. The organic solution was concentrated on a rotary evaporator to yield a yellow oil. The oil was distilled on a Kugelrohr apparatus (100-110 ° C @ 0.03 mm Hg) to yield a colorless oil. Analytical data are reported in Table I.

Example III

1-[1-Phenyl-2-(2-pyridyl)ethyl]piperidine

2-(2-pyridyl)acetophenone (4 gm) and p-toluenesulfonic acid (150 mg) were combined with toluene (50 ml). Piperidine (10 ml) was added all at once and the mixture heated to reflux. The heating was continued for 20 hours, with removal of the water that was generated during the condensation through use of a Dean-Stark trap. The reaction solution was allowed to cool to room temperature and the mixture concentrated on a rotary evaporator. The resulting yellow oil was distilled on a Kugelrohr apparatus (120 ° C @ 0.05 mm Hg) to yield a yellow oil. The oil was dissolved in ethanol (25 ml) and sodium borohydride (3 gm) was added to the solution. The solution was heated to reflux and the heating continued for 4 hours. The solution was allowed to cool to room temperature and was treated with water. The resulting solution was extracted with ether and the combined ether solutions washed with water. The ether solution was dried over magnesium

sulfate and concentrated on a rotary evaporator. The residue was distilled on a Kugelrohr apparatus (120 °C @ 0.05 mm Hg) to give the product as a yellow oil. Analytical data are reported in Table I.

Example IV

alpha-(1-phenylcyclohexyl)benzylamine

Phenylmagnesium bromide (18 ml, 3 M solution in tetrahydrofuran) was cooled to 0 °C under argon. A solution of 1-phenylcyclopropanecarbonitrile (7 gm) in toluene (50 ml) was added dropwise to the Grignard reagent. After the addition, the mixture was heated to reflux and the heating continued for 4 hours. The reaction mixture was cooled in an ice bath and treated dropwise with acetic acid (5 ml). The solid material was filtered and the filtrated concentrated on a rotary evaporator. The crude oil was dissolved in ethanol (50 ml) and treated all at once with sodium borohydride (3 gm). The solution was heated to reflux and the heating continued for 16 hours. The solution was allowed to cool to room temperature and concentrated on a rotary evaporator. The residue was dissolved in a mixture of ether and water and the layers separated. The ether solution was extracted with 6 N hydrochloric acid and the combined aqueous solutions were chilled in an ice bath and made basic with 10% sodium hydroxide. The aqueous solution was extracted with ether and the combined ether solutions were dried over magnesium sulfate, then concentrated on a rotary evaporator. The residue was distilled on a Kugelrohr apparatus (100 °C @ 0.03 mm Hg) to provide a colorless oil.

Example V

1-[1-(1-phenylcyclopropyl)benzyl]piperidine

Alpha-(1-phenylcyclohexyl)benzylamine (4 gm) was combined with potassium carbonate (2 gm) in acetonitrile (25 ml). 1,5-Dibromopentane was added to the mixture all at once and the mixture was heated to reflux. The heating was continued for 20 hours. The mixture was allowed to cool to room temperature and treated with water (50 ml). The solution was extracted with ether (3 X 75 ml) and the combined ether solutions washed with water (2 X 25 ml) and dried over magnesium sulfate. The ether solution was concentrated on a rotary evaporator and the residue distilled on a Kugelrohr apparatus (100 °C @ 0.03 mm Hg) to give a colorless oil. The oil was dissolved in cyclohexane and purified by preparative centrifugally accelerated radial thin layer chromatography on silica gel using 30% ethyl acetate in cyclohexane as an eluant to give the product as a colorless oil. Analytical data are reported in Table I.

Example VI

1,2-Diphenyl-2-(1-piperidinyl)ethanone

2-Bromo-2-phenylacetophenone (2 gm) was dissolved in acetonitrile (25 ml) and treated all at once with piperidine (5 ml). The solution was heated to reflux and the heating was continued for 2 hours. The mixture was allowed to cool to room temperature and was partitioned between ether (75 ml) and water (75 ml). The ether solution was extracted with 6 N hydrochloric acid (3 X 15 ml) and the combined acid solutions cooled in an ice bath. The cold acid solution was made basic with concentrated ammonium hydroxide and the mixture extracted with ether (3 X 25 ml). The combined ether solutions were dried over magnesium sulfate and concentrated on a rotary evaporator to give the product as a white foam. Analytical data are reported in

Table I.

Example VII

1-(1,2-Diphenyl-2-hydroxyethyl)piperidine

1,2-Diphenyl-2-(1-piperidyl)ethanone was dissolved in ethanol (15 ml) and treated all at once with sodium borohydride (0.5 g). The solution was heated to reflux and the heating continued for 16 hours. The reaction solution was allowed to cool to room temperature, treated with water (50 ml) and extracted with ether (3 X 50 ml). The combined ether solutions were dried over magnesium sulfate and concentrated on a rotary evaporator to a colorless oil. Analytical data are reported in Table I.

Example VIII

2,2-Dimethylphenylacetamide

2,2-Dimethylphenylacetic acid (5 gm) was combined with thionyl chloride (25 ml) and the solution heated to reflux. The heating was continued for 2 hours. The solution was allowed to cool to room temperature and the excess thionyl chloride removed by concentration on a rotary evaporator. The residue was suspended in cyclohexane (25 ml) and the solvent removed by evaporation on a rotary evaporator. The residue was added to cold ammonium hydroxide (50 ml) and the mixture stirred for two hours. The precipitate was filtered and dried in a vacuum to give the product as a white powder.

Example IX

2,2-Dimethyl-1,2-diphenylethylamine

2,2-Dimethyl-2-phenylacetamide (5 gm) was combined with phosphorus oxychloride and the solution heated to reflux. Heating was continued for 4 hours and the reaction mixture was allowed to cool to room temperature. The solution was poured onto ice and the resulting mixture extracted with ether. The combined ether extracts were dried over magnesium sulfate and concentrated on a rotary evaporator to yield a yellow oil. The oil was dissolved in toluene (50 ml) and added dropwise to a solution of phenylmagnesium bromide (8 ml, 3 M in tetrahydrofuran). The solution was heated to reflux and the heating continued for 4 hours. The reaction solution was cooled in an ice bath and treated with water (5 ml). The resulting mixture was filtered and the filtrated dried over magnesium sulfate and concentrated on a rotary evaporator. The resulting oil was dissolved in ethanol (50 ml) and treated with sodium borohydride (3 gm). The resulting solution was heated to reflux and the heating continued for 16 hours. The solution was allowed to cool to room temperature, treated with water (50 ml) and extracted with ether (3 X 100 ml). The combined ether extracts were dried over magnesium sulfate and concentrated on a rotary evaporator to yield a yellow oil. The oil was distilled on a Kugelrohr apparatus (100 $^{\circ}$ C @ 0.04 mm Hg) to obtain the product as a colorless oil.

Example X

1-(2,2-Dimethyl-1,2-diphenylethyl)piperidine

2,2-Dimethyl-1,2-diphenylethylamine (1 gm) was combined with potassium carbonate (2 gm) in acetonitrile (25 ml). 1,5- Dibromopentane (2 ml) was added to the mixture all at once and the mixture was heated to reflux. The heating was continued for 20 hours. The mixture was allowed to cool to room temperature and treated with water (50 ml). The solution was extracted with ether (3 X 75 ml) and the combined ether solutions washed with water (2 X 25 ml). The ether solution was extracted with 6 N hydrochloric acid (3 X 25 ml) and the combined acid solutions were cooled in an ice bath. The acid solution was made basic with 10% sodium hydroxide solution and the aqueous mixture extracted with ether (3 X 50 ml). The combined ether solutions were dried over magnesium sulfate and concentrated on a rotary evaporator. The residue was distilled on a Kugelrohr apparatus (120 ° C @ 0.01 mm Hg) to give a colorless oil. Analytical data are reported in Table I.

Example XI

2,2-Dimethyl-2-phenyl-1-(2-thienyl)ethanone

2,2-Dimethylphenylacetic acid (5 gm) was combined with phosphorus pentoxide (5 gm) in thiophene (25 ml). The solution was heated to reflux and the heating continued for 3 hours. The solution was allowed to cool to room temperature, treated with water (25 ml) and ether (50 ml) and the two layers were separated. The ether solution was extracted with 10% sodium hydroxide solution (2 X 25 ml). The ether solution was dried over magnesium sulfate and concentrated on a rotary evaporator. The residual oil was distilled on a Kugelrohr apparatus (80 ° C @ 0.05 mm Hg) to provide the product as an amber oil.

Example XII

2,2-Dimethyl-2-phenyl-1-(2-thienyl)ethanol

2,2-Dimethyl-2-phenyl-1-(2-thienyl)ethanone (1 gm) was dissolved in ethanol (50 ml) and treated with sodium borohydride (1 gm). The solution was heated to reflux and the heating continued for 17 hours. The solution was allowed to cool to room temperature and was concentrated on a rotary evaporator. The residue was dissolved in a mixture of water (25 ml) and ether (25 ml) and the resulting layers separated. The ether solution was dried over magnesium sulfate and concentrated on a rotary evaporator. The residue was distilled on a Kugelrohr apparatus (80 ° C @ 0.05 mm Hg) to give the product as a yellow oil.

Example XIII

1-[2,2-Dimethyl-2-phenyl-1-(2-thienyl)ethyl]piperidine

2,2-Dimethyl-2-phenyl-1-(2-thienyl)ethanol (0.8 gm) was combined with thionyl chloride (1 ml) and triethylamine (1 ml) in methylene chloride (25 ml). The solution was heated to reflux and the heating continued for 20 hours. The reaction mixture was allowed to cool to room temperature and was washed with water (2 X 15 ml). The organic solution was dried over magnesium sulfate and concentrated on a rotary evaporator. The resulting oil was dissolved in acetonitrile (25 ml) and treated with potassium carbonate (1 gm) and piperidine (1 ml). The mixture was heated to reflux and the heating continued for 22 hours. The

mixture was allowed to cool to room temperature and was treated with water (25 ml). The solution was extracted with ether (3 X 25 ml) and the combined ether solutions were extracted with 6 N hydrochloric acid (3 X 10 ml). The combined acid solutions were cooled in an ice bath and made basic by the addition of 15% sodium hydroxide solution. The aqueous solution was extracted with ether (3 X 25 ml) and the combined ether solutions were dried over magnesium sulfate and concentrated on a rotary evaporator. The resulting oil was distilled on a Kugelrohr apparatus (120° C @ 0.03 mm Hg) to give the product as a yellow oil. Analytical data are reported in Table I.

Example XIV

2-Phenyl-1-(2-thienyl)ethanone

Phenylacetic acid (5 gm) was combined with phosphorus pentoxide (5 gm) in thiophene (25 ml) and the mixture heated to reflux. The heating was continued for 2 hours, the reaction mixture was allowed to cool to room temperature. The solution was decanted from the solids into methylene chloride (25 ml). The organic solution was washed with 10% sodium hydroxide solution (2 X 10 ml) and dried over magnesium sulfate. The organic solution was concentrated on a rotary evaporator. The residue was distilled on a Kugelrohr apparatus (80° C @ 0.04 mm Hg) to give the product as a colorless oil which solidified upon standing.

Example XV

1-[2-Phenyl-1-(2-thienyl)ethyl]-1,2,3,6-tetrahydropyridine

2-Phenyl-1-(2-thienyl)ethanone (1 gm) was combined with 1,2,3,6-tetrahydropyridine (5 ml) in toluene (10 ml) and cooled in an ice bath. A solution of titanium tetrachloride (3 ml) in toluene (10 ml) was added dropwise to the cold solution of the ketone. After the addition, the reaction solution was heated to reflux and the heating continued for 1 hour. The solution was allowed to cool to room temperature and treated with water (25 ml). The resulting mixture was extracted with ether (3 X 25 ml) and the combined ether solutions were dried over magnesium sulfate and concentrated on a rotary evaporator. The residue was distilled on a Kugelrohr apparatus (100° C @ 0.04 mm Hg) to obtain a yellow oil. The oil was dissolved in ethanol (25 ml) and treated all at once with acetic acid (5 ml), followed by sodium cyanoborohydride (1 gm). The solution was heated to reflux and the heating continued for 16 hours. The solution was allowed to cool to room temperature and treated with water (50 ml). The resulting solution was extracted with ether (3 X 50 ml) and the combined ether solutions dried over magnesium sulfate and concentrated on a rotary evaporator. The residue was distilled on a Kugelrohr apparatus (110° C @ 0.03 mm Hg) to give a brown oil. The oil was dissolved in cyclohexane and the product purified by preparative centrifugally accelerated radial thin layer chromatography on silica gel using 30% ethyl acetate in cyclohexane as an eluant. The product was obtained as a yellow oil. Analytical data are reported in Table I.

Example XVI

1,2,-Diphenyl-1-butanone oxime

1,2,-Diphenyl-1-butanone was combined with hydroxylamine hydrochloride (5 gm) and sodium acetate (5 gm) in ethanol (100 ml) and the mixture heated to reflux. The heating was continued for 12 hours. The hot solution was treated with water until the solution became turbid. The solution was allowed to cool to

room temperature. The white crystals of product that separated during cooling were filtered and air dried.

Example XVII

1,2-Diphenyl-1-aminobutane

1,2,-Diphenyl-1-butanone oxime (2 gm) was combined with glacial acetic acid (2 ml) and 10% palladium on charcoal (100 mg) in ethanol (10 ml). The mixture was hydrogenated at 50 p.s.i at room temperature for 15 hours. The catalyst was removed by filtration and the filtrate was treated with water (50 ml). The solution was made basic by the addition of 10% sodium hydroxide solution and extracted with ether (3 X 50 ml). The combined ether solutions were extracted with 6 N hydrochloric acid (3 X 25 ml) and the combined acid solutions were made basic by the addition of 10% sodium hydroxide. This aqueous solution was extracted with ether (3 X 50 ml) and the combined ether solutions dried over magnesium sulfate and concentrated on a rotary evaporator to give the product as a yellow oil.

Example XVIII

1-(1,2-Diphenylbutyl)piperidine

1,2-Diphenyl-1-aminobutane (1.2 gm) was combined with potassium carbonate (2 gm) in acetonitrile (25 ml). The mixture was treated all at once with 1,5-dibromopentane (1.2 gm) and heated to reflux. Heating was continued for 20 hours. The mixture was allowed to cool to room temperature and treated with water (50 ml). The solution was extracted with ether (3 X 25 ml). The combined ether solutions were washed with water (2 X 25 ml) and dried over magnesium sulfate. The solution was concentrated on a rotary evaporator and the residue distilled on a Kugelrohr apparatus (100 °C @ 0.05 mm Hg) to obtain the product as a colorless oil. Analytical data are reported in Table I.

Example XIX

1-(1,2-Diphenylethyl)-1,2,3,6-tetrahydropyridine

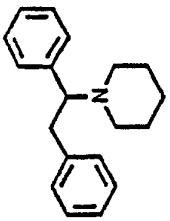
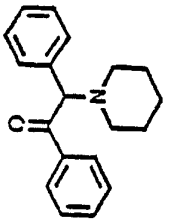
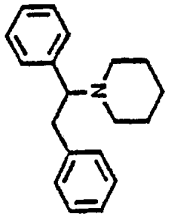
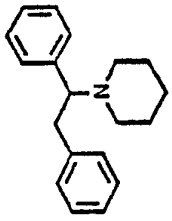
1,2-Diphenylethanol (3 gm) was combined with triethylamine (2.5 ml) in methylene chloride (50 ml). The solution was treated with thionyl chloride (1.22 ml) and stirred at room temperature for 2 hours. Water (20 ml) was added to the solution and the resulting layers separated. The methylene chloride solution was washed with water (20 ml) and dried over magnesium sulfate. The solution was concentrated on a rotary evaporator to give a colorless oil which solidified upon standing. This solid was combined with potassium carbonate (1 gm) in acetonitrile (25 ml) and treated with 1,2,3,6-tetrahydropyridine (5 ml). The mixture was heated to reflux and the heating continued for 20 hours. The mixture was allowed to cool to room temperature and a mixture of water (50 ml) and ether (75 ml) were added. The resulting layers were separated and the ether solution washed with water (2 X 25 ml). The ether solution was dried over magnesium sulfate and concentrated on a rotary evaporator. The residual oil was dissolved in ether (25 ml) and extracted with a solution of sulfuric acid (1 ml) in water (10 ml). The aqueous layer was chilled in an ice bath and made basic with solid sodium hydroxide. The resulting mixture was extracted with ether (3 X 20 ml) and the combined ether solutions dried over magnesium sulfate and concentrated on a rotary evaporator. The residue was distilled on a Kugelrohr apparatus (100 °C @ 0.05 mm Hg) to give the product as an amber oil. Analytical data are reported in Table I.

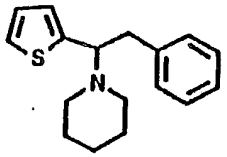
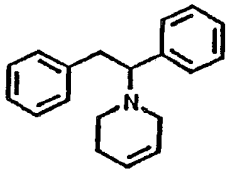
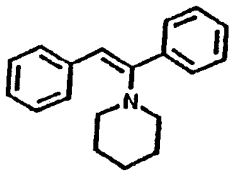
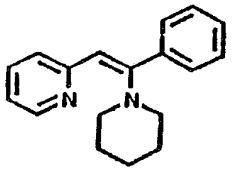
Example XX

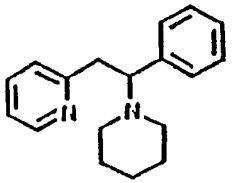
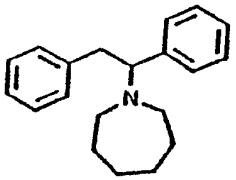
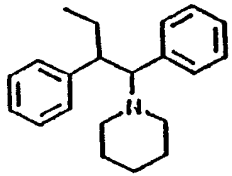
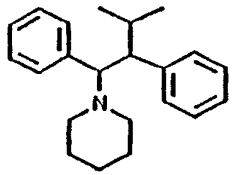
(+)- and (-)-1-(1,2-Diphenylethyl)piperidine

(±)-(1,2-Diphenylethyl)piperidine (1.5 gm) was combined with L-tartaric acid (0.84 gm) in water (25 ml) and heated to dissolve the solids. The solution was allowed to cool to room temperature to effect crystallization. The first crop of crystals were collected by filtration and designated (+)-(1,2-diphenylethyl)-piperidine. The filtrate was concentrated by heating to boiling on a hot plate. The solution was allowed to cool to room temperature to effect crystallization. The second crop of crystals were collected by filtration and designated (-)-(1,2-diphenylethyl)piperidine. The specific rotation for the (+)- isomer in methylene chloride is $[\alpha]_D$ = +1.4. The specific rotation for the (-)- isomer in methylene chloride is $[\alpha]_D$ = -1.4. Analytical data are reported in Table I.

Table I is a list of 33 specific compounds of most interest within Formula I. The preparation of 12 of the compounds in Table I is described in detail in Example Procedures I-XX, above. The remaining compounds may likewise be prepared in accordance with the above-described Example Procedures, as noted in Table I.

Compound Number	Name	Structure	Method of Preparation	Elemental Analysis Theo	Elemental Analysis Found	MP / BP (phys state)
1	(±)-1-(1,2-Diphenylethyl)-piperidine		II	C 85.40 H 8.75 N 5.24	85.26 9.03 5.31	100°C @ 0.05mmHg (Yellow Oil)
2	(±)-1,2-Diphenyl-2-(1-piperidinyl)ethanone		VI	NA		100°C @ 0.05mmHg (Oil)
3	(-)-1-(1,2-Diphenylethyl)-piperidine		XX	C 84.27 H 8.78 N 5.17	84.03 8.80 5.13	100°C @ 0.05mmHg (Oil)
4	(+)-1-(1,2-Diphenylethyl)-piperidine		XX	C 84.27 H 8.78 N 5.17	84.66 8.80 5.14	100°C @ 0.05mmHg (Oil)

Compound number	Name	Structure	Method of preparation	Elemental Analysis Theo	Found	MP / BP (phys state)
5	(±)-1-[2-Phenyl-1-(2-thienyl)-ethyl]piperidine Hydrosulfate		XIV,XV	C 54.46 H 6.34 N 3.73	54.48 6.12 3.69	>300°C (white solid)
6	(±)-1-(1,2-Diphenylethyl)-1,2,3,6-tetrahydropyridine		XIX	C 85.47 H 8.07 N 5.24	85.75 7.88 5.47	80°C @ 0.04mmHg (Yellow Oil)
7	1-(1,2-Diphenylethenyl)-piperidine		III	NA		80°C @ 0.04mmHg (Yellow Oil)
8	1-[Phenyl-2-(2-pyridinyl)-ethenyl]piperidine		III	NA		80°C @ 0.04mmHg (Yellow Oil)

Compound Number	Name	Structure	Method of Preparation	Elemental Analysis Theo	Found	MP / BP (phys state)
9	(±)-1-[1-Phenyl-2-(2-pyridinyl) ethyl]piperidine		III	C 81.15 H 8.32 N 10.51	80.73 8.33 10.38	120°C @ 0.05mmHg (Yellow Oil)
10	(±)-1-(1,2-Diphenylethyl)-1H-azepine		V	C 84.60 H 9.05 N 4.93	84.50 8.88 4.86	100°C @ 0.05mmHg (Yellow Oil)
11	(±)-1-(1,2-Diphenylbutyl)-piperidine		XI,XII,XIII	NA		120°C @ 0.05mmHg (Colorless Oil)
12	(±)-1-(1,2-Diphenyl-3-methyl-butyl)piperidine		XI,XII,XIII	NA		120°C @ 0.05mmHg (Colorless Oil)

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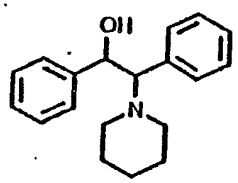
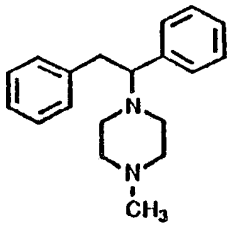
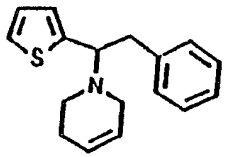
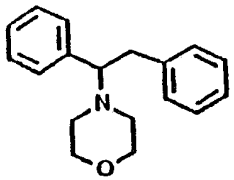
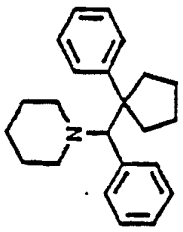
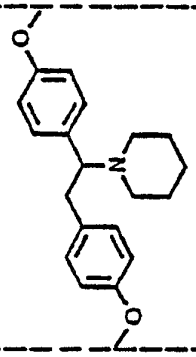
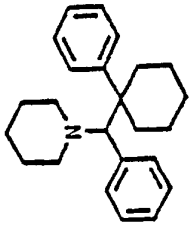
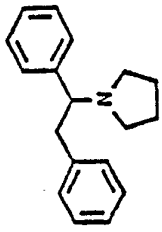
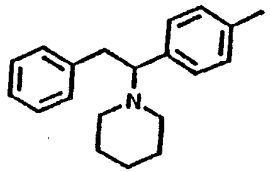
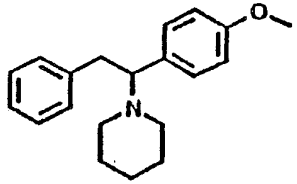
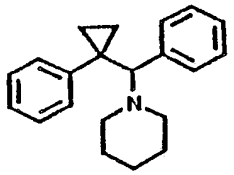
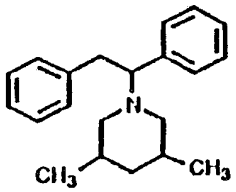
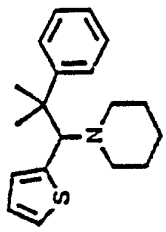
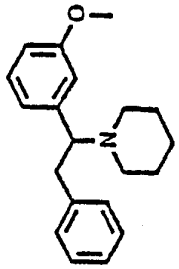
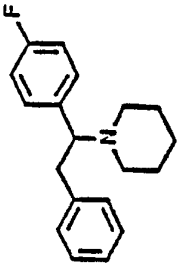
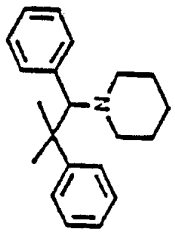
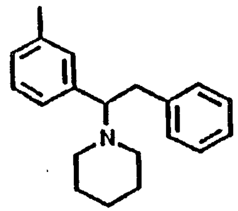
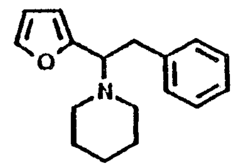
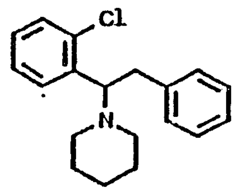
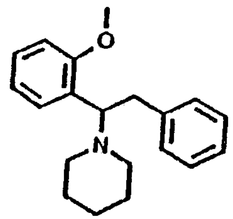
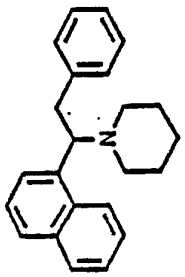
Compound Number	Name	Structure	Method of Preparation	Elemental Analysis Theo	Found	MP / BP (phys state)
13	(±)-1-(1,2-diphenyl-1-hydroxyethyl)piperidine		VI,VII	NA		110°C @ 0.05mmHg (Colorless Oil)
14	(±)-1-(1,2-Diphenylethyl)-4-methylpiperazine		II	C 81.38 H 8.62 N 9.98	81.41 8.74 9.72	120°C @ 0.05mmHg (Yellow Oil)
15	(±)-1-[2-Phenyl-1-(2-thienyl)-ethyl]-1,2,3,6-tetrahydropyridine		XIV,XV	C 74.79 H 7.16 N 5.13	74.41 6.94 5.11	110°C @ 0.03mmHg (Yellow Oil)
16	(±)-1-(1,2-Diphenylethyl)-morpholine		II	C 81.86 H 7.91 N 5.23	80.80 8.07 5.28	110°C @ 0.03mmHg (Colorless Oil)

Compound Number	Name	Structure	Method of Preparation	Elemental Analysis		MP / BP (phys state)
				Theo	Found	
17	(±)-1-[1-(1-Phenylcyclopentyl)benzyl]piperidine		IV,V	C 85.56 H 8.85 N 4.15	85.60 8.68 4.19	120°C @ 0.03mmHg (Colorless Oil)
18	(±)-1-[1,2-Di(4-methoxyphenyl)ethyl]piperidine		I, II	C 77.50 H 8.36 N 4.30	77.11 8.34 4.11	150°C @ 0.06mmHg (Yellow Oil)
19	(±)-1-[1-(1-Phenylcyclohexyl)benzyl]piperidine		IV,V	C 86.43 H 9.36 N 4.19	86.42 9.54 4.20	130°C @ 0.06mmHg (Yellow Oil)
20	(±)-1-(1,2-Diphenylethyl)-pyrrolidine		II	C 86.00 H 8.42 N 5.57	85.56 8.43 5.47	100°C @ 0.06mmHg (Colorless Oil)

Compound Number	Name	Structure	Method of Preparation	Elemental Analysis Theo	Found	MP / BP (phys state)
21	(±)-1-[1-(4-Methylphenyl)-2-phenylethyl]piperidine		I, II	C 84.87 H 9.04 N 4.94	84.60 9.26 5.29	100°C @ 0.03mmHg (Colorless Oil)
22	(±)-1-[1-(4-Methoxyphenyl)-2-phenylethyl]piperidine		I, II	C 79.85 H 8.57 N 4.65	79.89 8.87 4.95	100°C @ 0.03mmHg (Colorless Oil)
23	(±)-1-[1-(1-Phenylcyclopropyl)benzyl]piperidine		IV, V	C 86.01 H 8.60 N 4.77	86.05 8.52 4.70	120°C @ 0.03mmHg (Colorless Oil)
24	(±)-1-(1,2-Diphenylethyl)-3,5-dimethylpiperidine		II	C 85.95 H 9.27 N 4.77	85.68 9.35 4.83	100°C @ 0.03mmHg (Yellow Oil)

Compound Number	Name	Structure	Method of Preparation	Elemental Analysis	Theo	Found	MP / BP (phys state)
25	(±)-1-[2,2-Dimethyl-2-phenyl-1-(2-thienyl)ethyl]piperidine		XI,XII,XIII	C 74.12 H 9.14 N 5.08	74.08 9.16 5.06	120°C @ 0.03mmHg (Yellow Oil)
26	(±)-1-[1-(3-Methoxyphenyl)-2-phenylethyl]piperidine		I,II	C 81.31 H 8.53 N 4.74	81.11 8.47 4.77	120°C @ 0.01mmHg (Colorless Oil)
27	(±)-1-[1-(4-Fluorophenyl)-2-phenylethyl]piperidine		I,II	C 80.53 H 7.83 N 4.94	80.40 7.96 4.90	110°C @ 0.01mmHg (Colorless Oil)
28	(±)-1-(2,2-Dimethyl-1,2-diphenylethyl)piperidine		X,XI,XII	C 85.42 H 9.28 N 4.74	85.25 8.87 4.80	120°C @ 0.01mmHg (Colorless Oil)

Compound Number	Name	Structure	Method of Preparation	Elemental Analysis Theo	Elemental Analysis Found	MP / BP (phys state)
29	(±)-1-[1-(3-Methylphenyl)-2-phenylethyl]piperidine		I, II	C 85.97 H 9.02 N 5.01	85.69 9.25 5.07	100°C @ 0.05mHg (Colorless Oil)
30	(±)-1-[1-(2-Furyl)-2-phenyl-ethyl]piperidine		IV,V	C 78.84 H 8.32 N 5.40	78.82 8.29 5.15	100°C @ 0.05mmHg (Yellow Oil)
31	(±)-1-[1-(2-Chlorophenyl)-2-phenylethyl]piperidine		IV,V	C 80.82 H 8.54 N 4.70	80.85 8.59 4.55	120°C @ 0.04mmHg (Yellow Oil)
32	(±)-[1-(2-methoxyphenyl)-2-phenylethyl]piperidine		IV,V	C 76.10 H 7.39 N 4.67	75.91 7.46 4.60	100°C @ 0.05mmHg (Yellow Oil)

Compound Number	Name	Structure	Method of Preparation	Elemental Analysis Theo	Found	MP / BP (phys state)
33	(±)-1-[1-(1-Naphthyl)-2-phenylethyl]piperidine		IV,V	C 81.68 H 8.22 N 4.11	81.51 7.87 3.64	140°C @ 0.05mmHg (Yellow Oil)

BIOLOGICAL EVALUATION

Prevention of the neurodegenerative consequences associated with conditions of hypoxia or ischemia may be accomplished with administration of a compound of Formula I. In particular, the compounds 1-33 in Table I have been evaluated in biological assays to measure the inhibition of hypoxia- or ischemia-induced neuronal toxicity. Compounds 1-33, as well as some earlier-known PCP-agonist compounds, were evaluated by various in vivo and in vitro assays to determine compound activity as an NMDA antagonist or PCP agonist. These biological assays, described below, included a radioreceptor assay, a chronic hypoxic insult assay, an acute azide toxicity assay, an NMDA/KA/QUIS antagonist assay, a forebrain ischemia assay, and a behavioral assay.

Radioreceptor Assay

Compounds 1-33 were compared against PCP and TCP in an assay to determine the relative potency of the compounds interacting with PCP receptors. To determine the effect of the compounds in a PCP receptor assay, crude membrane preparations were prepared by homogenizing whole rat brains in 30 ml of ice-cold 5 mM Tris-HCl, pH 7.4 (Tris buffer), with a Brinkman Polytron (setting 6, 15 sec). The homogenate was centrifuged twice at 20,000 x g for 15 min at 4° C with an intervening resuspension of the pellet in cold Tris buffer. The final pellet was resuspended in Tris buffer to obtain a final concentration of 0.1 g of tissue per ml. Incubation tubes were prepared in triplicate and contained 0.1 ml of tissue suspension, 1 nM of ^{3}H-TCP and varying concentrations of displacing ligand (0.1 - 30,000 nM) in a final volume of 0.5 ml. After a 1 hour incubation, the contents of the test tubes were filtered through Schleier & Schuell #32 filters, which had been presoaked for at least 2 hours in 0.05% polyethyleneimine. The test tubes were rinsed twice and the filters once with 4 ml of tris buffer. Radioactivity on the filters was determined by liquid scintillation spectrometry. Specific binding was defined as the total amount of tritiated compound bound minus the amount bound in the presence of 10 μM of TCP compound. K_i values were determined using the method of Cheng & Prusoff [Biochem. Pharmacol., 22, 3099-3108 (1973)].

Table II

Test Compound	K_i apparent (nM) (units + SEM)
PCP	96 ± 15
TCP	20 ± 6
Compound No. 1	39 ± 11
Compound No. 2	1800 ± 100
Compound No. 3	2900 ± 600
Compound No. 4	25 ± 8
Compound No. 5	90 ± 20
Compound No. 6	54 ± 3
Compound No. 7	>30000
Compound No. 8	>30000
Compound No. 9	280 ± 40
Compound No. 10	180 ± 1
Compound No. 11	2300 ± 500
Compound No. 12	670 ± 30
Compound No. 13	410 ± 10
Compound No. 14	>30000
Compound No. 15	45 ± 14
Compound No. 16	4400 ± 100
Compound No. 17	4300 ± 200
Compound No. 18	>30000
Compound No. 19	690 ± 70

Compound No. 20	16000 ± 2600
Compound No. 21	1800 ± 300
Compound No. 22	8100 ± 500
Compound No. 23	>30000
Compound No. 24	850 ± 40
Compound No. 25	>30000
Compound No. 26	100 ± 20
Compound No. 27	220 ± 10
Compound No. 28	12000 ± 1000
Compound No. 29	110 ± 30
Compound No. 30	400 ± 10
Compound No. 31	0.19 ± 0.11
Compound No. 32	170 ± 10
Compound No. 33	6000 ± 1700

Chronic Hypoxic Insult Assay

Compound Nos. 4 and 5 were tested for their ability to protect hippocampal neurons from hypoxia-induced cell death. Cultures of hippocampal neurons were prepared from embryonic day 17 Sprague-Dawley rats. The hippocampi were dissociated into a single cell suspension by incubation with 0.25% trypsin, 40 mg/ml DNase followed by gentle trituration through a Pasteur pipet. The cells were plated in a polylysine-coated 96-well plate and maintained in a chemically defined medium until use. The cells were grown for 2 to 3 weeks in 5% CO_2-in-air humidified environment at 36°C to establish a thick network of neuronal processes with numerous spontaneously active synapses. Exposure to hypoxic/anoxic environment was accomplished by placing the cultures in an anaerobic chamber, and flushing it with a mixture of 95% N_2 + 5% CO_2 gas to rapidly drop the O_2 tension to near zero. The O_2 tension was maintained at near zero using a disposable H_2 + CO_2 generator envelope with palladium catalyst. Compound No. 4 and Compound No. 5 were added to the culture medium prior to incubation in the anaerobic chamber and maintained there for 6 hours. Following 2 hours of exposure to normal O_2 tension, the cultures were processed for morphological and quantitive biochemical neuronal cell viability assays.

The neuronal survival assay utilized the compound MTT [(3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide)], a pale yellow substrate that is cleaved by the mitochondrial enzyme succinate-dehydrogenase to yield a dark blue formazan product. This process requires active mitochondria, present only in live cells. Cultures of hippocampal neurons grown in 96-well plates were incubated with 1 mg/ml MTT at 36°C in a 10% CO_2-in-air incubator for 30-60 min. At the end of the incubation, a dark blue precipitate outlined only viable cells. The precipitate was then solubilized using 0.08 N HCl/isopropanol mixture and the absorbance measured with an ELISA plate reader (Dynatech MR600) using a test wavelength of 570 nm and a reference wavelength of 630 nm. The resulting optical density is directly proportional to the number of viable cells.

Maximum protection of neurons from hypoxic insult was obtained with 1μM of Compound No. 4 and with 10 μM of Compound No. 5:

Sample	Optical Density (units + SEM)
Untreated Control	0.058 ± 0.01
Hypoxia	0.020 ± 0.01
Hypoxia + 1 μM Compound No. 4	0.046 ± 0.01
Hypoxia + 10 μM Compound No. 5	0.047 ± 0.01

Acute Azide Toxicity Assay

Compound No. 4 was tested for its ability to protect hippocampal neurons from sodium azide poisoning which selectively kills mature neurons while sparing glial cells. Neuronal cells were prepared and the cell viability assays were performed as described in the chronic hypoxia insult assay, above.

Cultures were exposed to 10 μM sodium azide for 1 hour either in the presence or absence of Compound No. 4 and immediately thereafter processed for qualitative (morphological) and quantitative viability assay. Under this acute and severe toxicity conditions, 100 μM of Compound No. 4 afforded the neurons significant protection from all death.

Sample	Optical Density (units + SEM)
Control	0.123 ± 0.01
Sodium azide	0.075 ± 0.01
Sodium azide + 100 μM Compound No. 4	0.133 ± 0.01

NMDA/KA Antagonist Assay

A 15-day old chick embryo retina, incubated for 30 min. in a balanced salt solution (BSS) containing 1 mM Glu, developed a full lesion characteristic of an immature mouse retina following s.c. administration of Glu. Other excitotoxin agonists also produce acute lesions within 30 min., each agent being effective at a concentration proportional to its known excitatory and toxic potencies. The pattern of cellular degeneration is restricted in each case to the ganglion cell, inner plexiform and inner nuclear layers, but within these areas certain agonists induce different patterns of degeneration, the differences being most pronounced between NMA and KA. Three agonists were employed in the present test, each at a concentration established previously to be the lowest concentration required to consistently cause a fully-developed retinal lesion: KA (25 μM), Quis (50 μM), and NMA (200 μM). Compound No. 1, Compound No. 4, Compound No. 5 and other PCP-like compounds were tested at various concentrations for their ability to prevent KA, Quis or NMA neurotoxicity. Although partial blocking was observed for each antagonist at concentrations below the threshold for complete protection, the criterion used for comparing agents for antagonist potency was the concentration required to completely prevent KA, Quis or NMA from exerting any toxic activity in any specimen (n>6) studied at that concentration. Internal controls in each experiment consisted of at least six specimens being incubated with agonist alone. A typical toxic reaction had to be present in all controls and absent from all experimental specimens in order to qualify as a blocking effect. The method of tissue preparation was as follows: 15-day old chick embryos were decapitated and their eyes removed and cut into quadrants after excising the cornea and removing the lens, vitreous and iris. The retinal quadrants were then gently separated from the pigment epithelium and incubated for 30 min. at 37° C in BSS to which an agonist or agonist plus antagonist was added. The BSS contained 140 mM Na^+, 5.0 mM K^+, 0.5 mM Ca^{++}, 4.5 mM Mg^{++}, 150 mM Cl^-, 5.6 mM glucose and bicarbonate/phosphate buffer (pH 7.3). After incubation for 30 min., the retinal quadrants were fixed by immersion in phosphate-buffered solution containing 1.5% glutaraldehyde and 1% paraformaldehyde, then additionally fixed in 1% osmium tetroxide, dehydrated in graded ethanols, cleared in toluene and embedded in araldite. Sections were cut 1 micron thick on a Sorval ultratome and stained with methylene blue/Azure 11 for histopathological evaluation by light microscopy.

Table III

POTENCIES OF ANTAGONISTS IN BLOCKING NMV, KA OR QUIS NEUROTOXICITY			
Compounds were rated according to the minimal concentration (μM) required to provide total protection against NMA (200 μM), KA (25 μM) or Quis (50 μM). Antagonists were tested over a range of concentrations from 1000 μM downward until a minimal effective concentration was established.			
Potential antagonist	vs NMA	vs KA	vs Quis*
PCP	1 μM	No Activity	No Activity
Metaphit	50 μM	No Activity	No Activity
Compound No. 1	0.125 μM	No Activity	No Activity
Compound No. 4	0.25 μM	No Activity	No Activity
Compound No. 5	0.25μM	No Activity	No Activity
*@ up to 500 μM			

Behavioral Assay

Nine compounds were tested in comparison with PCP and TCP by an in vivo assay which determined stereotypic behavior in rats treated with the compounds. Male Sprague-Dawley rats weighing 200 to 250 g were used in the behavioral experiments. Each rat was used only once. Rats were anesthetized lightly with ether before a 20-gauge needle was used to make a hole in the rat's skull for i.c.v. injection of drugs at a later date.These rats were allowed to recover for at least 1 day before being used in the behavioral assays. On the day of the experiment, rats were placed individually into plastic rat cages and allowed at least 1 hr to acclimate before testing. Drugs were administered to rats in a random, single-blind fashion. Behavioral ratings were taken at 5-min intervals up to 1 hr after drug administration i.c.v., i.p., or s.c. using the PCP rating scale as described by Sturgeon et al [Sturgeon, R.D., Fessler, R.G. and Meltzer, H.Y., "Behavioral Rating Scales for Accessing Phencyclidine-Induced Locomotor Activity, Stereotyped Behavior And Ataxia In Rats", European J. Pharmacol. 59 169, (1970)].Briefly, the rating scale for stereotyped behavior is: 0, inactive or nonrepetitive activity; 1, sniffing, grooming or rearing; 2, nondirectional movements, and occasional reciprocal forepaw treading; 3, circling or head-weaving behavior or backpeddling; 4, rapid and continuous circling or head-weaving behavior, assuming a praying posture or gagging; and 5, dyskinetic extension and flexion of limbs, head and neck or head-weaving greater than in "4".

Dose-response curves for each treatment were determined at the time of maximal behavioral effect. Peak effects were found 5 min after i.c.v. administration of PCP (25-20000 nmol/rat). Peak effects of PCP (2.0-32 mg/kg) after i.p. administration were observed at 15 min. A rating of 5 in the PCP-rating scale was considered as complete stereotyped behavior, that is, a 100% response. At least 21 rats (at least seven rats/dose) were used to determine each dose-response curve and ED_{50} values. ED_{50} values and dose-response curves were evaluated using a computerized Finney assay [Statistical Methods In Biological Assays, 2nd Edn., Hatner Pub. Co., New York (1964)].

The ability of the tested compounds to induce stereotyped behavior was assessed at 2.5, 5 and 10 minutes and thereafter every 5 min up to 1 hr after i.c.v., i.p., or s.c. administration. Results are summarized in Table IV:

Table IV

	Stereotyped Behavior ED_{50}		
Test Compound	i.c.v.[a,b]	s.c.[c]	i.p.[d]
PCP	150(120-170)	NT	NT
Compound No. 1	220(140-210)	2.9(2.4-3.6)	2.0(1.1-3.3)
Compound No. 3	NT[e]	>40	NT
Compound No. 4	120(100-140)	0.78(0.60-1.0)	2.1(1.2-3.5)
Compound No. 5	NT	3.5(2.7-4.6)	NT
Compound No. 6	100(81-120)	NT	NT
Compound No. 12	NT	>50	NT
Compound No. 13	NT	11(8.2-14)	NT
Compound No. 15	NT	1.7(1.3-2.2)	NT
Compound No. 20	NT	7.8(5.7-11)	NT

[a] Numbers are in units of nmoles/rat
[b] Values in parenthesis are 95% confidence intervals
[c] Numbers are in units of mg/kg
[d] Numbers are in units of mg/kg
[e] NT = Not tested by this route

Forebrain Ischemia Assay

Male Mongolian gerbils, 50-70 gm, were used as subjects. Compound No. 1 (30 mg/kg) was injected i.p. 30 minutes prior to carotid occlusion into 6 gerbils. In preparation for surgical procedures, the animals were lightly anesthetized with methoxyflurane and placed upside down on a heated pad with their snout within a nosecone. Nitrous oxide (70%): oxygen (30%) plus 0.5% halothane was circulated through the nosecone to provide continuous anesthesia throughout the surgical procedure. A midline incision was made in the neck and the carotid arteries were exposed. A length of suture thread was placed under each carotid. The thread was then tightened around each carotid and pressure applied to the thread to insure flow was occluded. Flow was occluded for 4-5 minutes and then the thread was removed. The carotids were visually inspected to confirm that reflow had occurred. The wound was then closed with autoclips and the gerbils allowed to recover. Following surgery, the gerbils were kept alive for 7 days. They were anesthetized with 100 mg/kg sodium pentobarbital and perfused transcardially with saline (with heparin) followed by buffered formalin. The brain was removed, trimmed and prepared for histological processing. Sections (10 microns) were stained with thionin. At 7 days following the ischemic insult, damaged neurons have been cleared away by glia and the extent of damage can be ascertained within the vulnerable CA1 region of the hippocampus. The cell loss in CA1 was rated as 0 (no loss), 1 (unilateral damage), 2 (bilateral partial cell loss), or 3 (complete bilateral cell loss). The test animals were compared to a group of 69 saline injected gerbils. The groups were compared by the Mann-Whitney U test [*Elementary Applied Statistics* (New York: Wiley and Sons), 1965]. The cell loss was significantly reduced in the gerbils given Compound No. 1 ($p<0.01$).

Also embraced within this invention is a class of pharmaceutical compositions comprising one or more compounds of Formula I in association with one or more non-toxic, pharmaceutically acceptable carriers and/or diluents and/or adjuvants (collectively referred to herein as "carrier" materials) and, if desired, other active ingredients. The compounds of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. Therapeutically effective doses of the compounds of the present invention required to prevent or arrest the progress of the medical condition are readily ascertained by one of ordinary skill in the art. The compounds and composition may, for example, be administered intravascularly, intraperitoneally, subcutaneously, intramuscularly or topically.

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. These may with advantage contain an amount of active ingredient from about 1 to 250 mg,

preferably from about 25 to 150 mg. A suitable daily dose for a mammal may vary widely depending on the condition of the patient and other factors. However, a dose of from about 0.1 to 3000 mg/kg body weight, particularly from about 1 to 100 mg/kg body weight, may be appropriate.

The active ingredient may also be administered by injection as a composition wherein, for example, saline, dextrose or water may be used as a suitable carrier. A suitable daily dose is from about 0.1 to 100 mg/kg body weight injected per day in multiple doses depending on the disease being treated. A preferred daily dose would be from about 1 to 30 mg/kg body weight. Compounds indicated for prophylactic therapy will preferably be administered in a daily dose generally in a range from about 0.1 mg to about 100 mg per kilogram of body weight per day. A more preferred dosage will be a range from about 1 mg to about 100 mg per kilogram of body weight. Most preferred is a dosage in a range from about 1 to about 50 mg per kilogram of body weight per day. A suitable dose can be administered, in multiple sub-doses per day. These sub-doses may be administered in unit dosage forms. Typically, a dose or sub-dose may contain from about 1 mg to about 100 mg of active compound per unit dosage form. A more preferred dosage will contain from about 2 mg to about 50 mg of active compound per unit dosage form. Most preferred is a dosage form containing from about 3 mg to about 25 mg of active compound per unit dose.

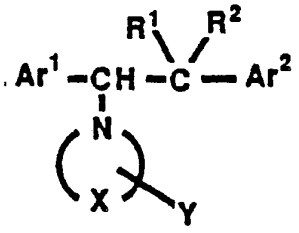
The dosage regimen for treating a disease condition with the compounds and/or compositions of this invention is selected in accordance with a variety of factors, including the type, age, weight, sex and medical condition of the patient, the severity of the disease, the route of administration, and the particular compound employed, and thus may vary widely.

For therapeutic purposes, the compounds of this invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered per os, the compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

Although this invention has been described with respect to specific embodiments, the details of these embodiments are not to be construed as limitations. Various equivalents, changes and modifications may be made without departing from the spirit and scope of this invention, and it is understood that such equivalent embodiments are part of this invention.

Claims

1. A compound of the formula



wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, hydroxyl, alkoxy, halo, cyano, nitro and mercapto, or wherein R^1 and R^2 may be taken together to form an oxo group or to form a saturated or partially unsaturated carbocyclic group having three to eight ring carbons; wherein each of Ar^1 and Ar^2 is a group independently selected from aryl and heteroaryl having one or two heteroatoms selected from N, O and S; and wherein any of the foregoing Ar^1 and Ar^2 groups having a substitutable position may be substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, alkenyl, alkynyl, hydroxyl, hydroxyalkyl, alkoxy,

alkoxyalkyl, amino, cyano, nitro and mercapto; wherein X is selected from CH, CH_2, NH, O and S, to form a ring having five to eight members provided that such ring is saturated or contains one double bond or is benzo-fused; and wherein Y is one or more a groups selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, alkenyl, alkynyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; or a pharmaceutically acceptable salt thereof;

with the proviso that when each of Ar^1 and Ar^2 is phenyl and each of R^1 and R^2 is hydrido or R^1 and R^2 together form oxo, then X cannot be a linear alkylene chain having four or five carbon atoms so as to form a racemic mixture;

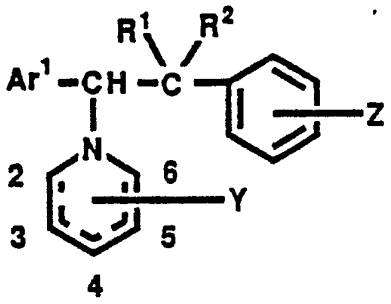
with the further proviso that when Ar^1 is thiophene, then X cannot be oxygen atom or a linear alkylene chain having five carbon atoms; and

with the further proviso that when Ar^1 is paramethylphenyl or para-methoxyphenyl and each of R^1 and R^2 is hydrido and Ar^2 is phenyl, then X cannot be a linear alkylene chain having five carbon atoms.

2. Compound of Claim 1 wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl, cycloalkyl, hydroxyl, halo and alkoxy, or wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to eight ring carbons; wherein each of Ar^1 and Ar^2 is independently selected from phenyl, thienyl, furanyl, pyridinyl, thiazolyl and naphthyl groups, and wherein any of the foregoing Ar^1 and Ar^2 groups having a substitutable position may be substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, alkenyl, alkynyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein X is selected from CH, CH_2, NH, O and S, to form a ring having five to eight members provided that such ring is saturated or contains one double bond; and wherein Y is a group selected from hydrido, alkyl, halo, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto.

3. Compound of Claim 2 wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl, cycloalkyl, hydroxyl, halo and alkoxy, or wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated cycloalkyl carbocyclic group having three to eight ring carbons; wherein each of Ar^1 and Ar^2 is a group independently selected from phenyl, thienyl, furanyl, pyridinyl, thiazolyl and naphthyl groups, and wherein any of the foregoing Ar^1 and Ar^2 groups may be substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, alkenyl, alkynyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein X is selected from CH or CH_2 to form a ring having five to seven members provided that such ring is saturated or contains one double bond; and wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy, amino, cyano, nitro and mercapto.

4. Compound of Claim 3 of the formula



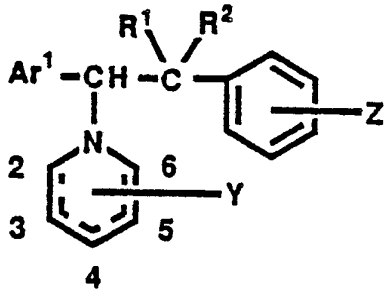
wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl, cycloalkyl, hydroxyl, halo and alkoxy, or wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to seven ring carbons; wherein Ar^1 is a group selected from phenyl, thienyl, furanyl, pyridinyl, thiazolyl and naphthyl groups, and wherein any of the foregoing Ar^1 groups having a substitutable position may be substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy and amino; and wherein Z is one or more groups selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto.

5. Compound of Claim 4 wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl, cycloalkyl, hydroxyl, halo and alkoxy, or wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to seven ring carbons; wherein Ar^1 is selected from phenyl, thienyl, pyridinyl and naphthyl groups, and wherein any of the foregoing Ar^1 groups having a substitutable position may be substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl,

halo, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy and amino; and wherein Z is one or more groups selected fromhydrido, alkyl, cycloalkyl, halo, hydroxyl, alkoxy and amino.

6. Compound of Claim 5 wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl and hydroxyl, or wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to six ring carbons; wherein Ar^1 is a group selected from phenyl, thienyl, pyridinyl and naphthyl groups, and wherein any of the foregoing Ar^1 groups having one or more substitutable position may be substituted with one or more radicals selected from hydrido, alkyl, halo, haloalkyl, hydroxyl, alkoxy, amino and nitro; wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy and amino; and wherein Z is one or more groups selected from hydrido, alkyl, halo, hydroxyl and alkoxy.

7. Compound of Claim 3 of the formula



wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl, cycloalkyl, hydroxyl, halo and alkoxy, or wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to seven ring carbons; wherein Ar^1 is a group selected from phenyl, thienyl, furanyl, pyridinyl, thiazolyl and naphthyl groups, and wherein any of the foregoing Ar^1 groups having a substitutable position is substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy and amino; wherein Z is one or more groups selected from alkyl, cycloalkyl, halo, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; and wherein the broken line within the N-containing ring represents a double bond between any two adjacent carbon atoms involving the 2-, 3-, 4-, 5-and 6-positions of the N-containing ring.

8. Compound of Claim 7 wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl, cycloalkyl, hydroxyl, halo and alkoxy, or wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to seven ring carbons; wherein Ar^1 is a group selected from phenyl, thienyl, furanyl, pyridinyl, thiazolyl and naphthyl groups, and wherein any of the foregoing groups having one or more substitutable positions may be substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy and amino; wherein Z is one or more groups selected from hydrido, alkyl, cycloalkyl, halo, hydroxyl, alkoxy and amino; and wherein the broken line within the N-containing ring represents a double bond between any two adjacent carbon atoms involving the 3-, 4-, 5-positions of the N-containing ring.

9. Compound of Claim 8 wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl, cycloalkyl, hydroxyl, halo and alkoxy; wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated cycloalkyl having three to seven ring carbons; wherein Ar^1 is selected from phenyl, thienyl, pyridinyl and naphthyl groups, and wherein any of the foregoing groups having a substitutable position is substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, hydroxyl, hydroxylalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy and amino; wherein Z is one or more groups selected from hydrido, alkyl, cycloalkyl, halo, hydroxyl, alkoxy and amino; and wherein the broken line within the N-containing ring represents either a double bond between any two adjacent carbon atoms involving the 3-, 4-, 5-positions of the N-containing ring.

10. Compound of Claim 9 wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl and hydroxyl; wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated cycloalkyl having three to six ring carbons; wherein Ar^1 is selected from phenyl, thienyl, pyridinyl and naphthyl groups, and wherein any of the foregoing groups having one or more substitutable positions is substituted with one or more radicals selected from hydrido, alkyl, halo, haloalkyl, hydroxyl, alkoxy, amino

and nitro; wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy and amino; wherein Z is one or more groups selected from hydrido, alkyl, halo, hydroxyl and alkoxy; and wherein the broken line within the N-containing ring represents either a double bond between any two adjacent carbon atoms involving the 3-, 4-, 5-positions of the N-containing ring.

11. Compound of Claim 3 selected from the group consisting of
(-)-1-(1,2-diphenylethyl)piperidine;
(+)-1-(1,2-diphenylethyl)piperidine;
1-(1,2-diphenylethenyl)piperidine;
(±)-1-[1-phenyl-2-(2-pyridinyl)ethyl]piperidine;
1-[1-phenyl-2-(2-pyridinyl)ethenyl]piperidine;
(±)-1-(1,2-diphenylethyl)-1H-azepine;
(±)-1-(1,2-diphenylbutyl)piperidine;
(±)-1-(1,2-diphenyl-3-methylbutyl)piperidine;
(±)-1-(1,2-diphenylethyl)-4-methylpiperazine;
(±)-1-(1,2-diphenylethyl)morpholine;
(±)-1-[1-(1-phenylcyclopentyl)benzyl]piperidine;
(±)-1-[1,2-di(4-methoxyphenyl)ethyl]piperidine;
(±)-1-[1-(1-phenylcyclohexyl)benzyl]piperidine;
(±)-1-[1-(1-phenylcyclopropyl)benzyl]piperidine;
(±)-1-(1,2-diphenylethyl)-3,5-dimethylpiperidine;
(±)-1-[2,2-dimethyl-2-phenyl-1-(2-thienyl)ethyl]piperidine;
(±)-1-[1-(3-methoxyphenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(4-fluorophenyl)-2-phenylethyl]piperidine;
(±)-1-(2,2-dimethyl-1,2-diphenylethyl)piperidine;
(±)-1-[1-(3-methylphenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(2-furyl)-2-phenylethyl]piperidine;
(±)-1-[1-(2-chlorophenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(2-methoxyphenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(1-naphthyl)-2-phenylethyl]piperidine;
(±)-1-(1,2-diphenylethyl)-1,2,3,6-tetrahydropyridine; and
(±)-1-[2-phenyl-1-(2-thienyl)ethyl]-1,2,3,6-tetrahydropyridine.

12. Compound of Claim 11 selected from the group consisting of
(-)-1-(1,2-diphenylethyl)piperidine;
(+)-1-(1,2-diphenylethyl)piperidine;
(±)-1-[1-phenyl-2-(2-pyridinyl)ethyl]piperidine;
(±)-1-(1,2-diphenylethyl)-1H-azepine;
(±)-1-(1,2-diphenylbutyl)piperidine;
(±)-1-(1,2-diphenylethyl)morpholine;
(±)-1-[1-(1-phenylcyclohexyl)benzyl]piperidine;
(±)-1-[1-(1-phenylcyclopropyl)benzyl]piperidine;
(±)-1-[1-(3-methoxyphenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(4-fluorophenyl)-2-phenylethyl]piperidine;
(±)-1-(2,2-dimethyl-1,2-diphenylethyl)piperidine;
(±)-1-[1-(3-methylphenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(2-chlorophenyl)-2-phenylethyl]piperidine; and
(±)-1-[1-(2-methoxyphenyl)-2-phenylethyl]piperidine.

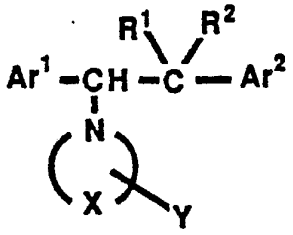
13. Compound of Claim 12 selected from the group consisting of
(±)-1-[1-(3-methoxyphenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(4-fluorophenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(3-methylphenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(2-chlorophenyl)-2-phenylethyl]piperidine; and
(±)-1-[1-(2-methoxyphenyl)-2-phenylethyl]piperidine.

14. Compound of Claim 13 which is
(±)-1-[1-(2-chlorophenyl)-2-phenylethyl]piperidine.

15. Compound of Claim 11 selected from the group consisting of
(±)-1-(1,2-diphenylethyl)-1,2,3,6-tetrahydropyridine;
and (±)-1-[2-phenyl-1-(2-thienyl)ethyl]-1,2,3,6-tetrahydropyridine.

16. Compound of Claim 15 which is
(±)-1-[2-phenyl-1-(2-thienyl)ethyl]-1,2,3,6-tetrahydropyridine.

17. A pharmaceutical composition comprising a therapeutically-effective amount of an active compound and a pharmaceutically-acceptable carrier or diluent, said active compound selected from a family of compounds of the formula

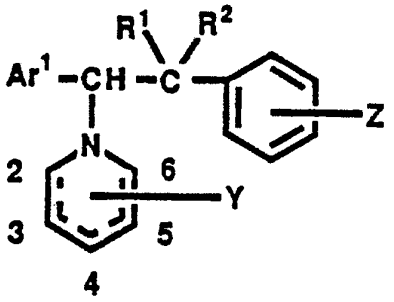


wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, hydroxyl, alkoxy, halo, cyano, nitro and mercapto, or wherein R^1 and R^2 may be taken together to form an oxo group or to form a saturated or partially unsaturated carbocyclic group having three to eight ring carbons; wherein each of Ar^1 and Ar^2 is a group independently selected from aryl and heteroaryl having one or two heteroatoms selected from N, O and S; and wherein any of the foregoing Ar^1 and Ar^2 groups having a substitutable position may be substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, alkenyl, alkynyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein X is selected from CH, CH_2, NH, O and S, to form a ring having five to eight members provided that such ring is saturated or contains one double bond or is benzo-fused; and wherein Y is one or more a groups selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, alkenyl, alkynyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; or a pharmaceutically acceptable salt thereof;
with the proviso that when each of Ar^1 and Ar^2 is phenyl and each of R^1 and R^2 is hydrido or R^1 and R^2 together form oxo, then X cannot be a linear alkylene chain having four or five carbon atoms so as to form a racemic mixture;
with the further proviso that when Ar^1 is thiophene, then X cannot be oxygen atom or a linear alkylene chain having five carbon atoms; and
with the further proviso that when Ar^1 is para-methylphenyl or para-methoxyphenyl and each of R^1 and R^2 is hydrido and Ar^2 is phenyl, then X cannot be a linear alkylene chain having five carbon atoms.

18. The composition of Claim 17 wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl, cycloalkyl, hydroxyl, halo and alkoxy, or wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to eight ring carbons; wherein each of Ar^1 and Ar^2 is independently selected from phenyl, thienyl, furanyl, pyridinyl, thiazolyl and naphthyl groups, and wherein any of the foregoing Ar^1 and Ar^2 groups having a substitutable position may be substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, alkenyl, alkynyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein X is selected from CH, CH_2, NH, O and S, to form a ring having five to eight members provided that such ring is saturated or contains one double bond; and wherein Y is a group selected from hydrido, alkyl, halo, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto.

19. The composition of Claim 18 wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl, cycloalkyl, hydroxyl, halo and alkoxy, or wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated cycloalkyl carbocyclic group having three to eight ring carbons; wherein each of Ar^1 and Ar^2 is a group independently selected from phenyl, thienyl, furanyl, pyridinyl, thiazolyl and naphthyl groups, and wherein any of the foregoing Ar^1 and Ar^2 groups may be substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, alkenyl, alkynyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein X is selected from CH or CH_2 to form a ring having five to seven members provided that such ring is saturated or contains one double bond; and wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy, amino, cyano, nitro and mercapto.

20. The composition of Claim 19 of the formula

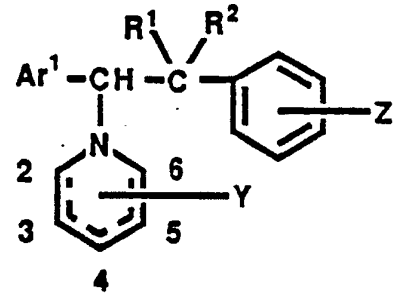


wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl, cycloalkyl, hydroxyl, halo and alkoxy, or wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to seven ring carbons; wherein Ar^1 is a group selected from phenyl, thienyl, furanyl, pyridinyl, thiazolyl and naphthyl groups, and wherein any of the foregoing Ar^1 groups having a substitutable position may be substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy and amino; and wherein Z is one or more groups selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto.

21. The composition of Claim 20 wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl, cycloalkyl, hydroxyl, halo and alkoxy, or wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to seven ring carbons; wherein Ar^1 is selected from phenyl, thienyl, pyridinyl and naphthyl groups, and wherein any of the foregoing Ar^1 groups having a substitutable position may be substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy and amino; and wherein Z is one or more groups selected from hydrido, alkyl, cycloalkyl, halo, hydroxyl, alkoxy and amino.

22. The composition of Claim 21 wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl and hydroxyl, or wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to six ring carbons; wherein Ar^1 is a group selected from phenyl, thienyl, pyridinyl and naphthyl groups, and wherein any of the foregoing Ar^1 groups having one or more substitutable position may be substituted with one or more radicals selected from hydrido, alkyl, halo, haloalkyl, hydroxyl, alkoxy, amino and nitro; wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy, amino; and wherein Z is one or more groups selected from hydrido, alkyl, halo, hydroxyl and alkoxy.

23. The composition of Claim 19 of the formula



wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl, cycloalkyl, hydroxyl, halo and alkoxy, or wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to seven ring carbons; wherein Ar^1 is a group selected from phenyl, thienyl, furanyl, pyridinyl, thiazolyl and naphthyl groups, and wherein any of the foregoing Ar^1 groups having a substitutable position is substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy and amino; wherein Z is one or more groups selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino,

cyano, nitro and mercapto; and wherein the broken line within the N-containing ring represents a double bond between any two adjacent carbon atoms involving the 2-, 3-, 4-, 5-and 6-positions of the N-containing ring.

24. The composition of Claim 23 wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl, cycloalkyl, hydroxyl, halo and alkoxy, or wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to seven ring carbons; wherein Ar^1 is a group selected from phenyl, thienyl, furanyl, pyridinyl, thiazolyl and naphthyl groups, and wherein any of the foregoing groups having one or more substitutable positions may be substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy and amino; wherein Z is one or more groups selected from hydrido, alkyl, cycloalkyl, halo, hydroxyl, alkoxy and amino; and wherein the broken line within the N-containing ring represents a double bond between any two adjacent carbon atoms involving the 3-, 4-, 5-positions of the N-containing ring.

25. The composition of Claim 24 wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl, cycloalkyl, hydroxyl, halo and alkoxy; wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated cycloalkyl having three to seven ring carbons; wherein Ar^1 is selected from phenyl, thienyl, pyridinyl and naphthyl groups, and wherein any of the foregoing groups having a substitutable position is substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, hydroxyl, hydroxylalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy and amino; wherein Z is one or more groups selected from hydrido, alkyl, cycloalkyl, halo, hydroxyl, alkoxy and amino; and wherein the broken line within the N-containing ring represents either a double bond between any two adjacent carbon atoms involving the 3-, 4-, 5-positions of the N-containing ring.

26. The composition of Claim 25 wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl and hydroxyl; wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated cycloalkyl having three to six ring carbons; wherein Ar^1 is selected from phenyl, thienyl, pyridinyl and naphthyl groups, and wherein any of the foregoing groups having one or more substitutable positions is substituted with one or more radicals selected from hydrido, alkyl, halo, haloalkyl, hydroxyl, alkoxy, amino and nitro; wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy and amino; wherein Z is one or more groups selected from hydrido, alkyl, halo, hydroxyl and alkoxy; and wherein the broken line within the N-containing ring represents either a double bond between any two adjacent carbon atoms involving the 3-, 4-, 5-positions of the N-containing ring.

27. The composition of Claim 19 wherein said active compound is selected from the group consisting of
(-)-1-(1,2-diphenylethyl)piperidine;
(+)-1-(1,2-diphenylethyl)piperidine;
1-(1,2-diphenylethenyl)piperidine;
(±)-1-[1-phenyl-2-(2-pyridinyl)ethyl]piperidine;
1-[1-phenyl-2-(2-pyridinyl)ethenyl]piperidine;
(±)-1-(1,2-diphenylethyl)-1H-azepine;
(±)-1-(1,2-diphenylbutyl)piperidine;
(±)-1-(1,2-diphenyl-3-methylbutyl)piperidine;
(±)-1-(1,2-diphenylethyl)-4-methylpiperazine;
(±)-1-(1,2-diphenylethyl)morpholine;
(±)-1-[1-(1-phenylcyclopentyl)benzyl]piperidine;
(±)-1-[1,2-di(4-methoxyphenyl)ethyl]piperidine;
(±)-1-[1-(1-phenylcyclohexyl)benzyl]piperidine;
(±)-1-[1-(1-phenylcyclopropyl)benzyl]piperidine;
(±)-1-(1,2-diphenylethyl)-3,5-dimethylpiperidine;
(±)-1-[2,2-dimethyl-2-phenyl-1-(2-thienyl)ethyl]piperidine;
(±)-1-[1-(3-methoxyphenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(4-fluorophenyl)-2-phenylethyl]piperidine;
(±)-1-(2,2-dimethyl-1,2-diphenylethyl)piperidine;
(±)-1-[1-(3-methylphenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(2-furyl)-2-phenylethyl]piperidine;
(±)-1-[1-(2-chlorophenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(2-methoxyphenyl)-2-phenylethyl]piperidine;

(±)-1-[1-(1-naphthyl)-2-phenylethyl]piperidine;
(±)-1-(1,2-diphenylethyl)-1,2,3,6-tetrahydropyridine; and
(±)-1-[2-phenyl-1-(2-thienyl)ethyl]-1,2,3,6-tetrahydropyridine.

28. The composition of Claim 27 wherein said active compound is selected from the group consisting of
(-)-1-(1,2-diphenylethyl)piperidine;
(+)-1-(1,2-diphenylethyl)piperidine;
(±)-1-[1-phenyl-2-(2-pyridinyl)ethyl]piperidine;
(±)-1-(1,2-diphenylethyl)-1H-azepine;
(±)-1-(1,2-diphenylbutyl)piperidine;
(±)-1-(1,2-diphenylethyl)morpholine;
(±)-1-[1-(1-phenylcyclohexyl)benzyl]piperidine;
(±)-1-[1-(1-phenylcyclopropyl)benzyl]piperidine;
(±)-1-[1-(3-methoxyphenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(4-fluorophenyl)-2-phenylethyl]piperidine;
(±)-1-(2,2-dimethyl-1,2-diphenylethyl)piperidine;
(±)-1-[1-(3-methylphenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(2-chlorophenyl)-2-phenylethyl]piperidine; and
(±)-1-[1-[2-methoxyphenyl)-2-phenylethyl]piperidine.

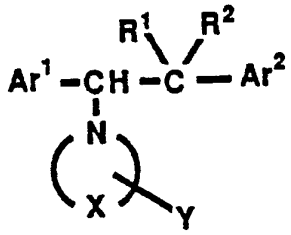
29. The composition of Claim 28 wherein said active compound is selected from the group consisting of
(±)-1-[1-(3-methoxyphenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(4-fluorophenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(3-methylphenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(2-chlorophenyl)-2-phenylethyl]piperidine; and
(±)-1-[1-(2-methoxyphenyl)-2-phenylethyl]piperidine.

30. The composition of Claim 29 wherein said active compound is
(±)-1-[1-(2-chlorophenyl)-2-phenylethyl]piperidine.

31. The composition of Claim 27 wherein said active compound is selected from the group consisting of
(±)-1-(1,2-diphenylethyl)-1,2,3,6-tetrahydropyridine;
and (±)-1-[2-phenyl-1-(2-thienyl)ethyl]-1,2,3,6-tetrahydropyridine.

32. The composition of Claim 31 wherein said active compound is
(±)-1-[2-phenyl-1-(2-thienyl)ethyl]-1,2,3,6-tetrahydropyridine.

33. Use of a compound of the formula



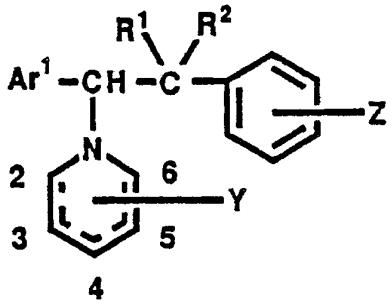
wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, hydroxyl, alkoxy, halo, cyano, nitro and mercapto, or wherein R^1 and R^2 may be taken together to form an oxo group or to form a saturated or partially unsaturated carbocyclic group having three to eight ring carbons; wherein each of Ar^1 and Ar^2 is a group independently selected from aryl and heteroaryl having one or two heteroatoms selected from N, O and S; and wherein any of the foregoing Ar^1 and Ar^2 groups having a substi tutable position may be substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, alkenyl, alkynyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein X is selected from CH, CH_2, NH, O and S, to form a ring having five to eight members provided that such ring is saturated or contains one double bond or is benzo-fused; and wherein Y is one or more a groups selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, alkenyl, alkynyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; or a pharmaceutically acceptable salt thereof for preparing a medicament to control neuropathological processes and the neurodegenerative consequences thereof in mammals.

34. Use according to Claim 33 wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl, cycloalkyl, hydroxyl, halo and alkoxy, or wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to eight ring carbons; wherein each of Ar^1

and Ar^2 is independently selected from phenyl, thienyl, furanyl, pyridinyl, thiazolyl and naphthyl groups, and wherein any of the foregoing Ar^1 and Ar^2 groups having a substitutable position may be substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, alkenyl, alkynyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein X is selected from CH, CH_2, NH, and S, to form a ring having five to eight members provided that such ring is saturated or contains one double bond; and wherein Y is a group selected from hydrido, alkyl, halo, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto.

35. Use according to Claim 34 wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl, cycloalkyl, hydroxyl, halo and alkoxy, or wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated cycloalkyl carbocyclic group having three to eight ring carbons; wherein each of Ar^1 and Ar^2 is a group independently selected from phenyl, thienyl, furanyl, pyridinyl, thiazolyl and naphthyl groups, and wherein any of the foregoing Ar^1 and Ar^2 groups may be substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, alkenyl, alkynyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein X is selected from CH or CH_2 to form a ring having five to seven members provided that such ring is saturated or contains one double bond; and wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy, amino, cyano, nitro and mercapto.

36. Use according to Claim 35 wherein the compound is of the formula

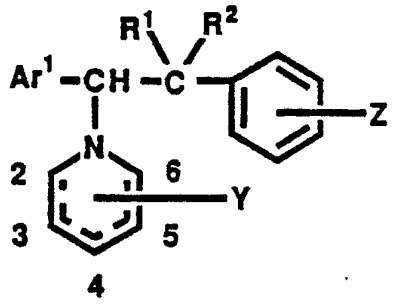


wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl, cycloalkyl, hydroxyl, halo and alkoxy, or wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to seven ring carbons; wherein Ar^1 is a group selected from phenyl, thienyl, furanyl, pyridinyl, thiazolyl and naphthyl groups, and wherein any of the foregoing Ar^1 groups having a substitutable position may be substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy and amino; and wherein Z is one or more groups selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto.

37. Use according to Claim 36 wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl, cycloalkyl, hydroxyl, halo and alkoxy, or wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to seven ring carbons; wherein Ar^1 is selected from phenyl, thienyl, pyridinyl and naphthyl groups, and wherein any of the foregoing Ar^1 groups having a substitutable position may be substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy and amino; and wherein Z is one or more groups selected from hydrido, alkyl, cycloalkyl, halo, hydroxyl, alkoxy and amino.

38. Use according to Claim 37 wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl and hydroxyl, or wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to six ring carbons; wherein Ar^1 is a group selected from phenyl, thienyl, pyridinyl and naphthyl groups, and wherein any of the foregoing Ar^1 groups having one or more substitutable position may be substituted with one or more radicals selected from hydrido, alkyl, halo, haloalkyl, hydroxyl, alkoxy, amino and nitro; wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy and amino; and wherein Z is one or more groups selected from hydrido, alkyl, halo, hydroxyl and alkoxy.

39. Use according to Claim 35 wherein the compound is of the formula



wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl, cycloalkyl, hydroxyl, halo and alkoxy, or wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to seven ring carbons; wherein Ar^1 is a group selected from phenyl, thienyl, furanyl, pyridinyl, thiazolyl and naphthyl groups, and wherein any of the foregoing Ar^1 groups having a substitutable position is substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy and amino; wherein Z is one or more groups selected from alkyl, cycloalkyl, halo, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; and wherein the broken line within the N-containing ring represents a double bond between any two adjacent carbon atoms involving the 2-, 3-, 4-, 5-and 6-positions of the N-containing ring.

40. Use according to Claim 39 wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl, cycloalkyl, hydroxyl, halo and alkoxy, or wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to seven ring carbons; wherein Ar^1 is a group selected from phenyl, thienyl, furanyl, pyridinyl, thiazolyl and naphthyl groups, and wherein any of the foregoing groups having one or more substitutable positions may be substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy and amino; wherein Z is one or more groups selected from hydrido, alkyl, cycloalkyl, halo, hydroxyl, alkoxy and amino; and wherein the broken line within the N-containing ring represents a double bond between any two adjacent carbon atoms involving the 3-, 4-, 5-positions of the N-containing ring.

41. Use according to Claim 40 wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl, cycloalkyl, hydroxyl, halo and alkoxy; wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated cycloalkyl having three to seven ring carbons; wherein Ar^1 is selected from phenyl, thienyl, pyridinyl and naphthyl groups, and wherein any of the foregoing groups having a substitutable position is substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, hydroxyl, hydroxylalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy and amino; wherein Z is one or more groups selected from hydrido, alkyl, cycloalkyl, halo, hydroxyl, alkoxy and amino; and wherein the broken line within the N-containing ring represents either a double bond between any two adjacent carbon atoms involving the 3-, 4-, 5-positions of the N-containing ring.

42. Use according to Claim 41 wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl and hydroxyl; wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated cycloalkyl having three to six ring carbons; wherein Ar^1 is selected from phenyl, thienyl, pyridinyl and naphthyl groups, and wherein any of the foregoing groups having one or more substitutable positions is substituted with one or more radicals selected from hydrido, alkyl, halo, haloalkyl, hydroxyl, alkoxy, amino and nitro; wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy and amino; wherein Z is one or more groups selected from hydrido, alkyl, halo, hydroxyl and alkoxy; and wherein the broken line within the N-containing ring represents either a double bond between any two adjacent carbon atoms involving the 3-, 4-, 5-positions of the N-containing ring.

43. Use according to Claim 34 wherein said compound is selected from the group consisting of (±)-1-(1,2-diphenylethyl)piperidine;
(±)-1,2-diphenyl-2-(1-piperidinyl)ethanone;
(-)-1-(1,2-diphenylethyl)piperidine;
(+)-1-(1,2-diphenylethyl)piperidine;
(±)-1-[2-phenyl-1-(2-thienyl)ethyl]piperidine hydrosulfate;
(±)-1-(1,2-diphenylethyl)-1,2,3,6-tetrahydropyridine;

1-(1,2-diphenylethenyl)piperidine;
1-[1-phenyl-2-(2-pyridinyl)ethenyl]piperidine;
(±)-1-[1-phenyl-2-(2-pyridinyl)ethyl]piperidine;
(±)-1-(1,2-diphenylethyl)-1H-azepine;
(±)-1-(1,2-diphenylbutyl)piperidine;
(±)-1-(1,2-diphenyl-3-methylbutyl)piperidine;
(±)-1-(1,2-diphenyl-1-hydroxyethyl)piperidine;
(±)-1-(1,2-diphenylethyl)-4-methylpiperazine;
(±)-1-[2-phenyl-1-(2-thienyl)ethyl]-1,2,3,6-tetrahydropyridine;
(±)-1-(1,2-diphenylethyl)morpholine;
(±)-1-[1-(1-phenylcyclopentyl)benzyl]piperidine;
(±)-1-[1,2-di(4-methoxyphenyl)ethyl]piperidine;
(±)-1-[1-(1-phenylcyclohexyl)benzyl]piperidine;
(±)-1-(1,2-diphenylethyl)pyrrolidine;
(±)-1-[1-(4-methylphenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(4-methoxyphenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(1-phenylcyclopropyl)benzyl]piperidine;
(±)-1-(1,2-diphenylethyl)-3,5-dimethylpiperidine;
(±)-1-[2,2-dimethyl-2-phenyl-1-(2-thienyl)ethyl]piperidine;
(±)-1-[1-(3-methoxyphenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(4-fluorophenyl)-2-phenylethyl]piperidine;
(±)-1-(2,2-dimethyl-1,2-diphenylethyl)piperidine;
(±)-1-[1-(3-methylphenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(2-furyl)-2-phenylethyl]piperidine;
(±)-1-[1-(2-chlorophenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(2-methoxyphenyl)-2-phenylethyl]piperidine; and
(±)-1-[1-(1-naphthyl)-2-phenylethyl]piperidine.

44. Use according to Claim 43 wherein said compound is selected from the group consisting of
(-)-1-(1,2-diphenylethyl)piperidine;
(+)-1-(1,2-diphenylethyl)piperidine;
1-(1,2-diphenylethenyl)piperidine;
(±)-1-[1-phenyl-2-(2-pyridinyl)ethyl]piperidine;
1-[1-phenyl-2-(2-pyridinyl)ethenyl]piperidine;
(±)-1-(1,2-diphenylethyl)-1H-azepine;
(±)-1-(1,2-diphenylbutyl)piperidine;
(±)-1-(1,2-diphenyl-3-methylbutyl)piperidine;
(±)-1-(1,2-diphenylethyl)-4-methylpiperazine;
(±)-1-(1,2-diphenylethyl)morpholine;
(±)-1-[1-(1-phenylcyclopentyl)benzyl]piperidine;
(±)-1-[1,2-di(4-methoxyphenyl)ethyl]piperidine;
(±)-1-[1-(1-phenylcyclohexyl)benzyl]piperidine;
(±)-1-[1-(1-phenylcyclopropyl)benzyl]piperidine;
(±)-1-(1,2-diphenylethyl)-3,5-dimethylpiperidine;
(±)-1-[2,2-dimethyl-2-phenyl-1-(2-thienyl)ethyl]piperidine;
(±)-1-[1-(3-methoxyphenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(4-fluorophenyl)-2-phenylethyl]piperidine;
(±)-1-(2,2-dimethyl-1,2-diphenylethyl)piperidine;
(±)-1-[1-(3-methylphenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(2-furyl)-2-phenylethyl]piperidine;
(±)-1-[1-(2-chlorophenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(2-methoxyphenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(1-naphthyl)-2-phenylethyl]piperidine;
(±)-1-(1,2-diphenylethyl)-1,2,3,6-tetrahydropyridine; and
(±)-1-[2-phenyl-1-(2-thienyl)ethyl]-1,2,3,6-tetrahydropyridine.

45. Use according to Claim 44 wherein said compound is selected from the group consisting of
(-)-1-(1,2-diphenylethyl)piperidine;
(+)-1-(1,2-diphenylethyl)piperidine;
(±)-1-[1-phenyl-2-(2-pyridinyl)ethyl]piperidine;

(±)-1-(1,2-diphenylethyl)-1H-azepine;
(±)-1-(1,2-diphenylbutyl)piperidine;
(±)-1-(1,2-diphenylethyl)morpholine;
(±)-1-[1-(1-phenylcyclohexyl)benzyl]piperidine;
(±)-1-[1-(1-phenylcyclopropyl)benzyl]piperidine;
(±)-1-[1-(3-methoxyphenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(4-fluorophenyl)-2-phenylethyl]piperidine;
(±)-1-(2,2-dimethyl-1,2-diphenylethyl)piperidine;
(±)-1-[1-(3-methylphenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(2-chlorophenyl)-2-phenylethyl]piperidine; and
(±)-1-[1-(2-methoxyphenyl)-2-phenylethyl]piperidine.

46. Use according to Claim 45 wherein said compound is selected from the group consisting of
(±)-1-[1-(3-methoxyphenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(4-fluorophenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(3-methylphenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(2-chlorophenyl)-2-phenylethyl]piperidine; and
(±)-1-[1-(2-methoxyphenyl)-2-phenylethyl]piperidine.

47. Use according to Claim 46 wherein said compound is
(±)-1-[1-(2-chlorophenyl)-2-phenylethyl]piperidine.

48. Use according to Claim 44 wherein said compound is selected from the group consisting of
(±)-1-(1,2-diphenylethyl)-1,2,3,6-tetrahydropyridine
and (±)-1-[2-phenyl-1-(2-thienyl)ethyl]-1,2,3,6-tetrahydropyridine.

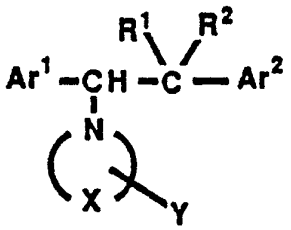
49. Use according to Claim 48 wherein said compound is
(±)-1-[2-phenyl-1-(2-thienyl)ethyl]-1,2,3,6-tetrahydropyridine.

50. Use according to Claim 33 for preparing a medicament for treating hypoxia, anoxia or ischemia.

51. Use according to Claim 50 for preparing a medicament for treating ischemia.

Claims for the following Contracting State: ES

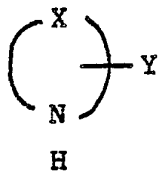
1. A process for preparing a compound of the formula



wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, hydroxyl, alkoxy, halo, cyano, nitro and mercapto, or wherein R^1 and R^2 may be taken together to form an oxo group or to form a saturated or partially unsaturated carbocyclic group having three to eight ring carbons; wherein each of Ar^1 and Ar^2 is a group independently selected from aryl and heteroaryl having one or two heteroatoms selected from N, O and S; and wherein any of the foregoing Ar^1 and Ar^2 groups having a substitutable position may be substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, alkenyl, alkynyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein X is selected from CH, CH_2, NH, O and S, to form a ring having five to eight members provided that such ring is saturated or contains one double bond or is benzo-fused; and wherein Y is one or more a groups selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, alkenyl, alkynyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; or a pharmaceutically acceptable salt thereof;
with the proviso that when each of Ar^1 and Ar^2 is phenyl and each of R^1 and R^2 is hydrido or R^1 and R^2 together form oxo, then X cannot be a linear alkylene chain having four or five carbon atoms so as to form a racemic mixture;
with the further proviso that when Ar^1 is thiophene, then X cannot be oxygen atom or a linear alkylene chain having five carbon atoms; and

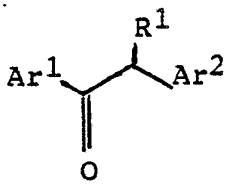
with the further proviso that when Ar^1 is para-methylphenyl or para-methoxyphenyl and each of R^1 and R^2 is hydrido and Ar^2 is phenyl, then X cannot be a linear alkylene chain having five carbon atoms,
characterized in that

A. an amine of the formula (2)



(2)

wherein Y and X are as defined before, is reacted in the presence of a Bronsted or Lewis acid in an appropriate solvent with a ketone of the formula (1)



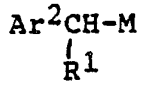
(1)

with Ar^1, Ar^2, R^1 as defined before, whereby said ketone (1) being prepared

a) by reaction of an nitrile of the formula (5)

Ar^1CN (5)

with an organometalic reagent of the formula (6)



(6)

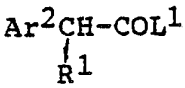
with Ar^1, Ar^2, R^1 as defined before and M being Li, MgCl, MgBr, CuCl, CuBr

or

b) by reaction of an arene of the formula (7)

Ar^1H (7)

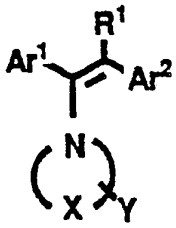
with a carboxylic acid derivative of the formula (8)



(8)

with Ar^1, Ar^2, R^1 as defined before and L^1 being an appropriate leaving group,

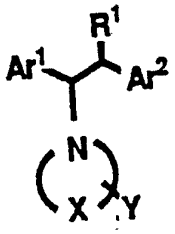
said reaction (A) generating the imine (3) of the formula



(3)

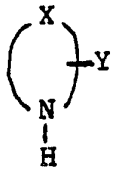
with all the substituents as defined before,

said imine (4) subsequently being transformed by reduction with an appropriate reducing agent in a solvent, yielding the desired compound of the formula



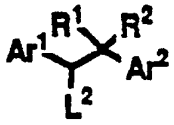
or

B) by reacting an amine of the formula (2)

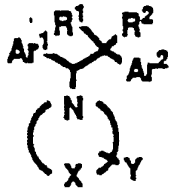


(2)

with X and Y as defined before,
either neat or in a solvent with a compound of the formula (9)

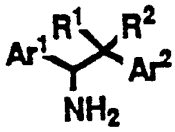


with Ar^1, Ar^2, R^1, R^2 as defined before and L^2 being an appropriate leaving group,
whereby said compound of the formula (9) being generated from the corresponding ketone,
yielding the desired compounds of the formula



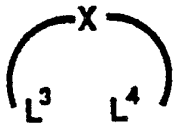
with all the substituents as defined,
or

C) by reacting a compound of the formula (12)



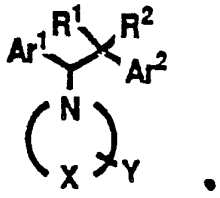
with all the substituents as defined before, and generated from the corresponding ketone, or from the reaction of the nitrile (1) AR^1CN with a compound of the formula

with the substituents as defined, with a compound of the formula (13)



(13)

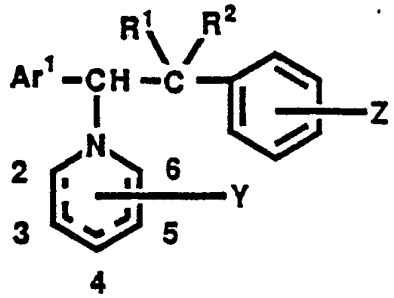
wherein X is as defined before and L^3 and L^4 being good leaving groups, yielding the desired compounds of the formula



2. Process according to Claim 1 wherein each of R^1 and R^2 of the compound prepared is a group independently selected from hydrido, alkyl, cycloalkyl, hydroxyl, halo and alkoxy, or wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to eight ring carbons; wherein each of Ar^1 and Ar^2 is independently selected from phenyl, thienyl, furanyl, pyridinyl, thiazolyl and naphthyl groups, and wherein any of the foregoing Ar^1 and Ar^2 groups having a substitutable position may be substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, alkenyl, alkynyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein X is selected from CH, CH_2, NH, O and S, to form a ring having five to eight members provided that such ring is saturated or contains one double bond; and wherein Y is a group selected from hydrido, alkyl, halo, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto.

3. Process according to Claim 2 wherein each of R^1 and R^2 of the compound prepared is a group independently selected from hydrido, alkyl, cycloalkyl, hydroxyl, halo and alkoxy, or wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated cycloalkyl carbocyclic group having three to eight ring carbons; wherein each of Ar^1 and Ar^2 is a group independently selected from phenyl, thienyl, furanyl, pyridinyl, thiazolyl and naphthyl groups, and wherein any of the foregoing Ar^1 and Ar^2 groups may be substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, alkenyl, alkynyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein X is selected from CH or CH_2 to form a ring having five to seven members provided that such ring is saturated or contains one double bond; and wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy, amino, cyano, nitro and mercapto.

4. Process according to Claim 3 wherein the compound prepared is of the formula



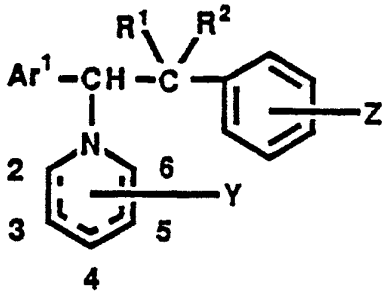
wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl, cycloalkyl, hydroxyl, halo and alkoxy, or wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to seven ring carbons; wherein Ar^1 is a group selected from phenyl, thienyl, furanyl, pyridinyl, thiazolyl and naphthyl groups, and wherein any of the foregoing Ar^1 groups having a substitutable position may be substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy and amino; and wherein Z is one or more groups

selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto.

5. Process according to Claim 4 wherein each of R^1 and R^2 of the compound prepared is a group independently selected from hydrido, alkyl, cycloalkyl, hydroxyl, halo and alkoxy, or wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to seven ring carbons; wherein Ar^1 is selected from phenyl, thienyl, pyridinyl and naphthyl groups, and wherein any of the foregoing Ar^1 groups having a substitutable position may be substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy and amino; and wherein Z is one or more groups selected from hydrido, alkyl, cycloalkyl, halo, hydroxyl, alkoxy and amino.

6. Process according to Claim 5 wherein each of R^1 and R^2 of the compound prepared is a group independently selected from hydrido, alkyl and hydroxyl, or wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to six ring carbons; wherein Ar^1 is a group selected from phenyl, thienyl, pyridinyl and naphthyl groups, and wherein any of the foregoing Ar^1 groups having one or more substitutable position may be substituted with one or more radicals selected from hydrido, alkyl, halo, haloalkyl, hydroxyl, alkoxy, amino and nitro; wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy and amino; and wherein Z is one or more groups selected from hydrido, alkyl, halo, hydroxyl and alkoxy.

7. Process according to Claim 3 wherein the compound prepared is of the formula



wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl, cycloalkyl, hydroxyl, halo and alkoxy, or wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to seven ring carbons; wherein Ar^1 is a group selected from phenyl, thienyl, furanyl, pyridinyl, thiazolyl and naphthyl groups, and wherein any of the foregoing Ar^1 groups having a substitutable position is substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy and amino; wherein Z is one or more groups selected from alkyl, cycloalkyl, halo, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; and wherein the broken line within the N-containing ring represents a double bond between any two adjacent carbon atoms involving the 2-, 3-, 4-, 5-and 6-positions of the N-containing ring.

8. Process according to Claim 7 wherein each of R^1 and R^2 of the compound prepared is a group independently selected from hydrido, alkyl, cycloalkyl, hydroxyl, halo and alkoxy, or wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to seven ring carbons; wherein Ar^1 is a group selected from phenyl, thienyl, furanyl, pyridinyl, thiazolyl and naphthyl groups, and wherein any of the foregoing groups having one or more substitutable positions may be substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy and amino; wherein Z is one or more groups selected from hydrido, alkyl, cycloalkyl, halo, hydroxyl, alkoxy and amino; and wherein the broken line within the N-containing ring represents a double bond between any two adjacent carbon atoms involving the 3-, 4-, 5-positions of the N-containing ring.

9. Process according to Claim 8 wherein each of R^1 and R^2 of the compound prepared is a group independently selected from hydrido, alkyl, cycloalkyl, hydroxyl, halo and alkoxy; wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated cycloalkyl having three to seven ring carbons; wherein Ar^1 is selected from phenyl, thienyl, pyridinyl and naphthyl groups, and wherein any of the foregoing groups having a substitutable position is substituted with one or more radicals selected from

hydrido, alkyl, cycloalkyl, halo, haloalkyl, hydroxyl, hydroxylalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy and amino; wherein Z is one or more groups selected from hydrido, alkyl, cycloalkyl, halo, hydroxyl, alkoxy and amino; and wherein the broken line within the N-containing ring represents either a double bond between any two adjacent carbon atoms involving the 3-, 4-, 5-positions of the N-containing ring.

10. Process according to Claim 9 wherein each of R^1 and R^2 of the compound prepared is a group independently selected from hydrido, alkyl and hydroxyl; wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated cycloalkyl having three to six ring carbons; wherein Ar^1 is selected from phenyl, thienyl, pyridinyl and naphthyl groups, and wherein any of the foregoing groups having one or more substitutable positions is substituted with one or more radicals selected from hydrido, alkyl, halo, haloalkyl, hydroxyl, alkoxy, amino and nitro; wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy and amino; wherein Z is one or more groups selected from hydrido, alkyl, halo, hydroxyl and alkoxy; and wherein the broken line within the N-containing ring represents either a double bond between any two adjacent carbon atoms involving the 3-, 4-, 5-positions of the N-containing ring.

11. Process according to Claim 3 wherein the compound prepared is selected from the group consisting of

(-)-1-(1,2-diphenylethyl)piperidine;
(+)-1-(1,2-diphenylethyl)piperidine;
1-(1,2-diphenylethenyl)piperidine;
(±)-1-[1-phenyl-2-(2-pyridinyl)ethyl]piperidine;
1-[1-phenyl-2-(2-pyridinyl)ethenyl]piperidine;
(±)-1-(1,2-diphenylethyl)-1H-azepine;
(±)-1-(1,2-diphenylbutyl)piperidine;
(±)-1-(1,2-diphenyl-3-methylbutyl)piperidine;
(±)-1-(1,2-diphenylethyl)-4-methylpiperazine;
(±)-1-(1,2-diphenylethyl)morpholine;
(±)-1-[1-(1-phenylcyclopentyl)benzyl]piperidine;
(±)-1-[1,2-di(4-methoxyphenyl)ethyl]piperidine;
(±)-1-[1-(1-phenylcyclohexyl)benzyl]piperidine;
(±)-1-[1-(1-phenylcyclopropyl)benzyl]piperidine;
(±)-1-(1,2-diphenylethyl)-3,5-dimethylpiperidine;
(±)-1-[2,2-dimethyl-2-phenyl-1-(2-thienyl)ethyl]piperidine;
(±)-1-[1-(3-methoxyphenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(4-fluorophenyl)-2-phenylethyl]piperidine;
(±)-1-(2,2-dimethyl-1,2-diphenylethyl)piperidine;
(±)-1-[1-(3-methylphenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(2-furyl)-2-phenylethyl]piperidine;
(±)-1-[1-(2-chlorophenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(2-methoxyphenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(1-naphthyl)-2-phenylethyl]piperidine;
(±)-1-(1,2-diphenylethyl)-1,2,3,6-tetrahydropyridine; and
(±)-1-[2-phenyl-1-(2-thienyl)ethyl]-1,2,3,6-tetrahydropyridine.

12. Process according to Claim 11 wherein the compound prepared is selected from the group consisting of

(-)-1-(1,2-diphenylethyl)piperidine;
(+)-1-(1,2-diphenylethyl)piperidine;
(±)-1-[1-phenyl-2-(2-pyridinyl)ethyl]piperidine;
(±)-1-(1,2-diphenylethyl)-1H-azepine;
(±)-1-(1,2-diphenylbutyl)piperidine;
(±)-1-(1,2-diphenylethyl)morpholine;
(±)-1-[1-(1-phenylcyclohexyl)benzyl]piperidine;
(±)-1-[1-(1-phenylcyclopropyl)benzyl]piperidine;
(±)-1-[1-(3-methoxyphenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(4-fluorophenyl)-2-phenylethyl]piperidine;
(±)-1-(2,2-dimethyl-1,2-diphenylethyl)piperidine;
(±)-1-[1-(3-methylphenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(2-chlorophenyl)-2-phenylethyl]piperidine; and
(±)-1-[1-(2-methoxyphenyl)-2-phenylethyl]piperidine.

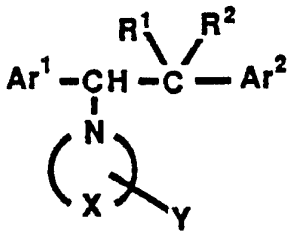
13. Process according to Claim 12 wherein the compound prepared is selected from the group consisting of
(±)-1-[1-(3-methoxyphenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(4-fluorophenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(3-methylphenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(2-chlorophenyl)-2-phenylethyl]piperidine; and
(±)-1-[1-(2-methoxyphenyl)-2-phenylethyl]piperidine.

14. Process according to Claim 13 wherein the compound prepared is
(±)-1-[1-(2-chlorophenyl)-2-phenylethyl]piperidine.

15. Process according to Claim 11 wherein the compound prepared is selected from the group consisting of
(±)-1-(1,2-diphenylethyl)-1,2,3,6-tetrahydropyridine;
and (±)-1-[2-phenyl-1-(2-thienyl)ethyl]-1,2,3,6-tetrahydropyridine.

16. Process according to Claim 15 wherein the compound prepared is
(±)-1-[2-phenyl-1-(2-thienyl)ethyl]-1,2,3,6-tetrahydropyridine.

17. Use of a compound of the formula

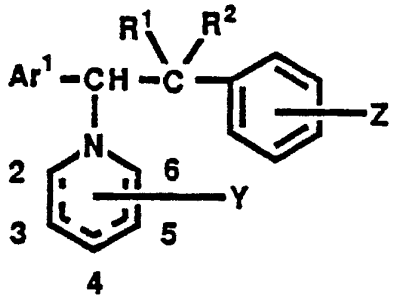


wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, hydroxyl, alkoxy, halo, cyano, nitro and mercapto, or wherein R^1 and R^2 may be taken together to form an oxo group or to form a saturated or partially unsaturated carbocyclic group having three to eight ring carbons; wherein each of Ar^1 and Ar^2 is a group independently selected from aryl and heteroaryl having one or two heteroatoms selected from N, O and S; and wherein any of the foregoing Ar^1 and Ar^2 groups having a substitutable position may be substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, alkenyl, alkynyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein X is selected from CH, CH_2, NH, O and S, to form a ring having five to eight members provided that such ring is saturated or contains one double bond or is benzo-fused; and wherein Y is one or more a groups selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, alkenyl, alkynyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; or a pharmaceutically acceptable salt thereof;
with the proviso that when each of Ar^1 and Ar^2 is phenyl and each of R^1 and R^2 is hydrido or R^1 and R^2 together form oxo, then X cannot be a linear alkylene chain having four or five carbon atoms so as to form a racemic mixture;
with the further proviso that when Ar^1 is thiophene, then X cannot be oxygen atom or a linear alkylene chain having five carbon atoms; and
with the further proviso that when Ar^1 is para-methylphenyl or para-methoxyphenyl and each of R^1 and R^2 is hydrido and Ar^2 is phenyl, then X cannot be a linear alkylene chain having five carbon atoms, for preparing a medicament for controlling neuropathological processes and the neurodegenerative consequences thereof in mammals.

18. Use according to Claim 17 wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl, cycloalkyl, hydroxyl, halo and alkoxy, or wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to eight ring carbons; wherein each of Ar^1 and Ar^2 is independently selected from phenyl, thienyl, furanyl, pyridinyl, thiazolyl and naphthyl groups, and wherein any of the foregoing Ar^1 and Ar^2 groups having a substitutable position may be substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, alkenyl, alkynyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein X is selected from CH, CH_2, NH, O and S, to form a ring having five to eight members provided that such ring is saturated or contains one double bond; and wherein Y is a group selected from hydrido, alkyl, halo, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto.

19. Use according to Claim 18 wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl, cycloalkyl, hydroxyl, halo and alkoxy, or wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated cycloalkyl carbocyclic group having three to eight ring carbons; wherein each of Ar^1 and Ar^2 is a group independently selected from phenyl, thienyl, furanyl, pyridinyl, thiazolyl and naphthyl groups, and wherein any of the foregoing Ar^1 and Ar^2 groups may be substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, alkenyl, alkynyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein X is selected from CH or CH_2 to form a ring having five to seven members provided that such ring is saturated or contains one double bond; and wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy, amino, cyano, nitro and mercapto.

20. Use according to Claim 19 wherein the compound is of the formula

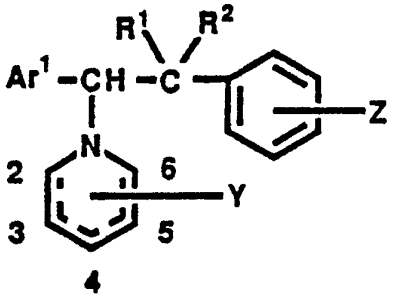


wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl, cycloalkyl, hydroxyl, halo and alkoxy, or wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to seven ring carbons; wherein Ar^1 is a group selected from phenyl, thienyl, furanyl, pyridinyl, thiazolyl and naphthyl groups, and wherein any of the foregoing Ar^1 groups having a substitutable position may be substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy and amino; and wherein Z is one or more groups selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto.

21. Use according to Claim 20 wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl, cycloalkyl, hydroxyl, halo and alkoxy, or wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to seven ring carbons; wherein Ar^1 is selected from phenyl, thienyl, pyridinyl and naphthyl groups, and wherein any of the foregoing Ar^1 groups having a substitutable position may be substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy and amino; and wherein Z is one or more groups selected from hydrido, alkyl, cycloalkyl, halo, hydroxyl, alkoxy and amino.

22. Use according to Claim 21 wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl and hydroxyl, or wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to six ring carbons; wherein Ar^1 is a group selected from phenyl, thienyl, pyridinyl and naphthyl groups, and wherein any of the foregoing Ar^1 groups having one or more substitutable position may be substituted with one or more radicals selected from hydrido, alkyl, halo, haloalkyl, hydroxyl, alkoxy, amino and nitro; wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy, amino; and wherein Z is one or more groups selected from hydrido, alkyl, halo, hydroxyl and alkoxy.

23. Use according to Claim 19 wherein the compound is of the formula



wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl, cycloalkyl, hydroxyl, halo and alkoxy, or wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to seven ring carbons; wherein Ar^1 is a group selected from phenyl, thienyl, furanyl, pyridinyl, thiazolyl and naphthyl groups, and wherein any of the foregoing Ar^1 groups having a substitutable position is substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy and amino; wherein Z is one or more groups selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; and wherein the broken line within the N-containing ring represents a double bond between any two adjacent carbon atoms involving the 2-, 3-, 4-, 5-and 6-positions of the N-containing ring.

24. Use according to Claim 23 wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl, cycloalkyl, hydroxyl, halo and alkoxy, or wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to seven ring carbons; wherein Ar^1 is a group selected from phenyl, thienyl, furanyl, pyridinyl, thiazolyl and naphthyl groups, and wherein any of the foregoing groups having one or more substitutable positions may be substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy and amino; wherein Z is one or more groups selected from hydrido, alkyl, cycloalkyl, halo, hydroxyl, alkoxy and amino; and wherein the broken line within the N-containing ring represents a double bond between any two adjacent carbon atoms involving the 3-, 4-, 5-positions of the N-containing ring.

25. Use according to Claim 24 wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl, cycloalkyl, hydroxyl, halo and alkoxy; wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated cycloalkyl having three to seven ring carbons; wherein Ar^1 is selected from phenyl, thienyl, pyridinyl and naphthyl groups, and wherein any of the foregoing groups having a substitutable position is substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, hydroxyl, hydroxylalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy and amino; wherein Z is one or more groups selected from hydrido, alkyl, cycloalkyl, halo, hydroxyl, alkoxy and amino; and wherein the broken line within the N-containing ring represents either a double bond between any two adjacent carbon atoms involving the 3-, 4-, 5-positions of the N-containing ring.

26. Use according to Claim 25 wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl and hydroxyl; wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated cycloalkyl having three to six ring carbons; wherein Ar^1 is selected from phenyl, thienyl, pyridinyl and naphthyl groups, and wherein any of the foregoing groups having one or more substitutable positions is substituted with one or more radicals selected from hydrido, alkyl, halo, haloalkyl, hydroxyl, alkoxy, amino and nitro; wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy and amino; wherein Z is one or more groups selected from hydrido, alkyl, halo, hydroxyl and alkoxy; and wherein the broken line within the N-containing ring represents either a double bond between any two adjacent carbon atoms involving the 3-, 4-, 5-positions of the N-containing ring.

27. Use according to Claim 19 wherein said active compound is selected from the group consisting of
(-)-1-(1,2-diphenylethyl)piperidine;
(+)-1-(1,2-diphenylethyl)piperidine;
1-(1,2-diphenylethenyl)piperidine;
(±)-1-[1-phenyl-2-(2-pyridinyl)ethyl]piperidine;
1-[1-phenyl-2-(2-pyridinyl)ethenyl]piperidine;

(±)-1-(1,2-diphenylethyl)-1H-azepine;
(±)-1-(1,2-diphenylbutyl)piperidine;
(±)-1-(1,2-diphenyl-3-methylbutyl)piperidine;
(±)-1-(1,2-diphenylethyl)-4-methylpiperazine;
(±)-1-(1,2-diphenylethyl)morpholine;
(±)-1-[1-(1-phenylcyclopentyl)benzyl]piperidine;
(±)-1-[1,2-di(4-methoxyphenyl)ethyl]piperidine;
(±)-1-[1-(1-phenylcyclohexyl)benzyl]piperidine;
(±)-1-[1-(1-phenylcyclopropyl)benzyl]piperidine;
(±)-1-(1,2-diphenylethyl)-3,5-dimethylpiperidine;
(±)-1-[2,2-dimethyl-2-phenyl-1-(2-thienyl)ethyl]piperidine;
(±)-1-[1-(3-methoxyphenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(4-fluorophenyl)-2-phenylethyl]piperidine;
(±)-1-(2,2-dimethyl-1,2-diphenylethyl)piperidine;
(±)-1-[1-(3-methylphenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(2-furyl)-2-phenylethyl]piperidine;
(±)-1-[1-(2-chlorophenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(2-methoxyphenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(1-naphthyl)-2-phenylethyl]piperidine;
(±)-1-(1,2-diphenylethyl)-1,2,3,6-tetrahydropyridine; and
(±)-1-[2-phenyl-1-(2-thienyl)ethyl]-1,2,3,6-tetrahydropyridine.

28. Use according to Claim 27 wherein said active compound is selected from the group consisting of
(-)-1-(1,2-diphenylethyl)piperidine;
(+)-1-(1,2-diphenylethyl)piperidine;
(±)-1-[1-phenyl-2-(2-pyridinyl)ethyl]piperidine;
(±)-1-(1,2-diphenylethyl)-1H-azepine;
(±)-1-(1,2-diphenylbutyl)piperidine;
(±)-1-(1,2-diphenylethyl)morpholine;
(±)-1-[1-(1-phenylcyclohexyl)benzyl]piperidine;
(±)-1-[1-(1-phenylcyclopropyl)benzyl]piperidine;
(±)-1-[1-(3-methoxyphenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(4-fluorophenyl)-2-phenylethyl]piperidine;
(±)-1-(2,2-dimethyl-1,2-diphenylethyl)piperidine;
(±)-1-[1-(3-methylphenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(2-chlorophenyl)-2-phenylethyl]piperidine; and
(±)-1-[1-(2-methoxyphenyl)-2-phenylethyl]piperidine.

29. Use according to Claim 28 wherein said active compound is selected from the group consisting of
(±)-1-[1-(3-methoxyphenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(4-fluorophenyl)-2-phenylethyl]piperidine;
(±)-1-[1- 3-methylphenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(2-chlorophenyl)-2-phenylethyl]piperidine; and
(±)-1-[1-(2-methoxyphenyl)-2-phenylethyl]piperidine.

30. Use according to Claim 29 wherein said active compound is
(±)-1-[1-(2-chlorophenyl)-2-phenylethyl]piperidine.

31. Use according to Claim 27 wherein said active compound is selected from the group consisting of
(±)-1-(1,2-diphenylethyl)-1,2,3,6-tetrahydropyridine;
and (±)-1-[2-phenyl-1-(2-thienyl)ethyl]-1,2,3,6-tetrahydropyridine.

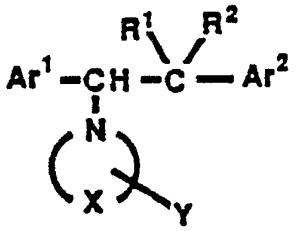
32. Use according to Claim 31 wherein said active compound is
(±)-1-[2-phenyl-1-(2-thienyl)ethyl]-1,2,3,6-tetrahydropyridine.

33. Use according to Claim 18 for preparing a medicament for treating hypoxia, anoxia or ischemia.

34. Use according to Claim 33 for preparing a medicament for treating ischemia.

Claims for the following Contracting State: GR

1. A compound of the formula



wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, hydroxyl, alkoxy, halo, cyano, nitro and mercapto, or wherein R^1 and R^2 may be taken together to form an oxo group or to form a saturated or partially unsaturated carbocyclic group having three to eight ring carbons; wherein each of Ar^1 and Ar^2 is a group independently selected from aryl and heteroaryl having one or two heteroatoms selected from N, O and S; and wherein any of the foregoing Ar^1 and Ar^2 groups having a substitutable position may be substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, alkenyl, alkynyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein X is selected from CH, CH_2, NH, O and S, to form a ring having five to eight members provided that such ring is saturated or contains one double bond or is benzo-fused; and wherein Y is one or more a groups selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, alkenyl, alkynyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; or a pharmaceutically acceptable salt thereof;

with the proviso that when each of Ar^1 and Ar^2 is phenyl and each of R^1 and R^2 is hydrido or R^1 and R^2 together form oxo, then X cannot be a linear alkylene chain having four or five carbon atoms so as to form a racemic mixture;

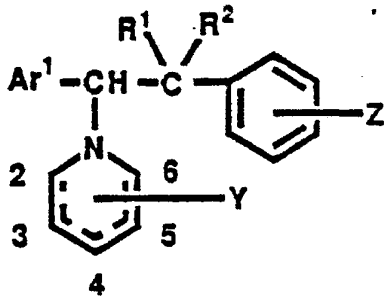
with the further proviso that when Ar^1 is thiophene, then X cannot be oxygen atom or a linear alkylene chain having five carbon atoms; and

with the further proviso that when Ar^1 is para-methylphenyl or para-methoxyphenyl and each of R^1 and R^2 is hydrido and Ar^2 is phenyl, then X cannot be a linear alkylene chain having five carbon atoms.

2. Compound of Claim 1 wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl, cycloalkyl, hydroxyl, halo and alkoxy, or wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to eight ring carbons; wherein each of Ar^1 and Ar^2 is independently selected from phenyl, thienyl, furanyl, pyridinyl, thiazolyl and naphthyl groups, and wherein any of the foregoing Ar^1 and Ar^2 groups having a substitutable position may be substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, alkenyl, alkynyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein X is selected from CH, CH_2, NH, O and S, to form a ring having five to eight members provided that such ring is saturated or contains one double bond; and wherein Y is a group selected from hydrido, alkyl, halo, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto.

3. Compound of Claim 2 wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl, cycloalkyl, hydroxyl, halo and alkoxy, or wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated cycloalkyl carbocyclic group having three to eight ring carbons; wherein each of Ar^1 and Ar^2 is a group independently selected from phenyl, thienyl, furanyl, pyridinyl, thiazolyl and naphthyl groups, and wherein any of the foregoing Ar^1 and Ar^2 groups may be substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, alkenyl, alkynyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein X is selected from CH or CH_2 to form a ring having five to seven members provided that such ring is saturated or contains one double bond; and wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy, amino, cyano, nitro and mercapto.

4. Compound of Claim 3 of the formula

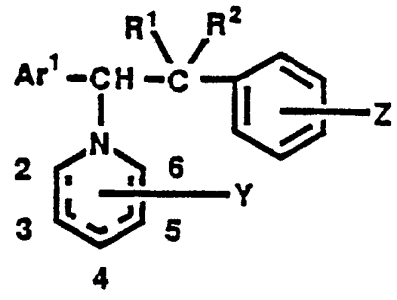


wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl, cycloalkyl, hydroxyl, halo and alkoxy, or wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to seven ring carbons; wherein Ar^1 is a group selected from phenyl, thienyl, furanyl, pyridinyl, thiazolyl and naphthyl groups, and wherein any of the foregoing Ar^1 groups having a substitutable position may be substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy and amino; and wherein Z is one or more groups selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto.

5. Compound of Claim 4 wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl, cycloalkyl, hydroxyl, halo and alkoxy, or wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to seven ring carbons; wherein Ar^1 is selected from phenyl, thienyl, pyridinyl and naphthyl groups, and wherein any of the foregoing Ar^1 groups having a substitutable position may be substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy and amino; and wherein Z is one or more groups selected from hydrido, alkyl, cycloalkyl, halo, hydroxyl, alkoxy and amino.

6. Compound of Claim 5 wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl and hydroxyl, or wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to six ring carbons; wherein Ar^1 is a group selected from phenyl, thienyl, pyridinyl and naphthyl groups, and wherein any of the foregoing Ar^1 groups having one or more substitutable position may be substituted with one or more radicals selected from hydrido, alkyl, halo, haloalkyl, hydroxyl, alkoxy, amino and nitro; wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy and amino; and wherein Z is one or more groups selected from hydrido, alkyl, halo, hydroxyl and alkoxy.

7. Compound of Claim 3 of the formula



wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl, cycloalkyl, hydroxyl, halo and alkoxy, or wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to seven ring carbons; wherein Ar^1 is a group selected from phenyl, thienyl, furanyl, pyridinyl, thiazolyl and naphthyl groups, and wherein any of the foregoing Ar^1 groups having a substitutable position is substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy and amino; wherein Z is one or more groups selected from alkyl, cycloalkyl, halo, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; and wherein the broken line within the N-containing ring represents a double bond

between any two adjacent carbon atoms involving the 2-, 3-, 4-, 5-and 6-positions of the N-containing ring.

8. Compound of Claim 7 wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl, cycloalkyl, hydroxyl, halo and alkoxy, or wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to seven ring carbons; wherein Ar^1 is a group selected from phenyl, thienyl, furanyl, pyridinyl, thiazolyl and naphthyl groups, and wherein any of the foregoing groups having one or more substitutable positions may be substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy and amino; wherein Z is one or more groups selected from hydrido, alkyl, cycloalkyl, halo, hydroxyl, alkoxy and amino; and wherein the broken line within the N-containing ring represents a double bond between any two adjacent carbon atoms involving the 3-, 4-, 5-positions of the N-containing ring.

9. Compound of Claim 8 wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl, cycloalkyl, hydroxyl, halo and alkoxy; wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated cycloalkyl having three to seven ring carbons; wherein Ar^1 is selected from phenyl, thienyl, pyridinyl and naphthyl groups, and wherein any of the foregoing groups having a substitutable position is substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, hydroxyl, hydroxylalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy and amino; wherein Z is one or more groups selected from hydrido, alkyl, cycloalkyl, halo, hydroxyl, alkoxy and amino; and wherein the broken line within the N-containing ring represents either a double bond between any two adjacent carbon atoms involving the 3-, 4-, 5-positions of the N-containing ring.

10. Compound of Claim 9 wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl and hydroxyl; wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated cycloalkyl having three to six ring carbons; wherein Ar^1 is selected from phenyl, thienyl, pyridinyl and naphthyl groups, and wherein any of the foregoing groups having one or more substitutable positions is substituted with one or more radicals selected from hydrido, alkyl, halo, haloalkyl, hydroxyl, alkoxy, amino and nitro; wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy and amino; wherein Z is one or more groups selected from hydrido, alkyl, halo, hydroxyl and alkoxy; and wherein the broken line within the N-containing ring represents either a double bond between any two adjacent carbon atoms involving the 3-, 4-, 5-positions of the N-containing ring.

11. Compound of Claim 3 selected from the group consisting of
(-)-1-(1,2-diphenylethyl)piperidine;
(+)-1-(1,2-diphenylethyl)piperidine;
1-(1,2-diphenylethenyl)piperidine;
(±)-1-[1-phenyl-2-(2-pyridinyl)ethyl]piperidine;
1-[1-phenyl-2-(2-pyridinyl)ethenyl]piperidine;
(±)-1-(1,2-diphenylethyl)-1H-azepine;
(±)-1-(1,2-diphenylbutyl)piperidine;
(±)-1-(1,2-diphenyl-3-methylbutyl)piperidine;
(±)-1-(1,2-diphenylethyl)-4-methylpiperazine;
(±)-1-(1,2-diphenylethyl)morpholine;
(±)-1-[1-(1-phenylcyclopentyl)benzyl]piperidine;
(±)-1-[1,2-di(4-methoxyphenyl)ethyl]piperidine;
(±)-1-[1-(1-phenylcyclohexyl)benzyl]piperidine;
(±)-1-[1-(1-phenylcyclopropyl)benzyl]piperidine;
(±)-1-(1,2-diphenylethyl)-3,5-dimethylpiperidine;
(±)-1-[2,2-dimethyl-2-phenyl-1-(2-thienyl)ethyl]piperidine;
(±)-1-[1-(3-methoxyphenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(4-fluorophenyl-2-phenylethyl]piperidine;
(±)-1-(2,2-dimethyl-1,2-diphenylethyl)piperidine;
(±)-1-[1-(3-methylphenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(2-furyl)-2-phenylethyl]piperidine;
(±)-1-[1-(2-chlorophenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(2-methoxyphenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(1-naphthyl)-2-phenylethyl]piperidine;
(±)-1-(1,2-diphenylethyl)-1,2,3,6-tetrahydropyridine; and
(±)-1-[2-phenyl-1-(2-thienyl)ethyl]-1,2,3,6-tetrahydropyridine.

12. Compound of Claim 11 selected from the group consisting of
(-)-1-(1,2-diphenylethyl)piperidine;
(+)-1-(1,2-diphenylethyl)piperidine;
(±)-1-[1-phenyl-2-(2-pyridinyl)ethyl]piperidine;
(±)-1-(1,2-diphenylethyl)-1H-azepine;
(±)-1-(1,2-diphenylbutyl)piperidine;
(±)-1-(1,2-diphenylethyl)morpholine;
(±)-1-[1-(1-phenylcyclohexyl)benzyl]piperidine;
(±)-1-[1-(1-phenylcyclopropyl)benzyl]piperidine;
(±)-1-[1-(3-methoxyphenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(4-fluorophenyl)-2-phenylethyl]piperidine;
(±)-1-(2,2-dimethyl-1,2-diphenylethyl)piperidine;
(±)-1-[1-(3-methylphenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(2-chlorophenyl)-2-phenylethyl]piperidine; and
(±)-1-[1-(2-methoxyphenyl)-2-phenylethyl]piperidine.

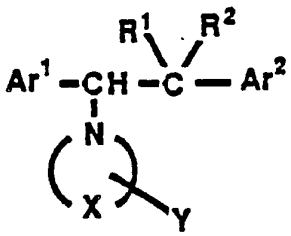
13. Compound of Claim 12 selected from the group consisting of
(±)-1-[1-(3-methoxyphenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(4-fluorophenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(3-methylphenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(2-chlorophenyl)-2-phenylethyl]piperidine; and
(±)-1-[1-(2-methoxyphenyl)-2-phenylethyl]piperidine.

14. Compound of Claim 13 which is
(±)-1-[1-(2-chlorophenyl)-2-phenylethyl]piperidine.

15. Compound of Claim 11 selected from the group consisting of
(±)-1-(1,2-diphenylethyl)-1,2,3,6-tetrahydropyridine;
and (±)-1-[2-phenyl-1-(2-thienyl)ethyl]-1,2,3,6-tetrahydropyridine.

16. Compound of Claim 15 which is
(±)-1-[2-phenyl-1-(2-thienyl)ethyl]-1,2,3,6-tetrahydropyridine.

17. Use of a compound of the formula



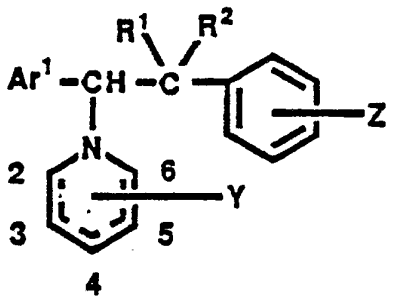
wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, hydroxyl, alkoxy, halo, cyano, nitro and mercapto, or wherein R^1 and R^2 may be taken together to form an oxo group or to form a saturated or partially unsaturated carbocyclic group having three to eight ring carbons; wherein each of Ar^1 and Ar^2 is a group independently selected from aryl and heteroaryl having one or two heteroatoms selected from N, O and S; and wherein any of the foregoing Ar^1 and Ar^2 groups having a substitutable position may be substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, alkenyl, alkynyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein X is selected from CH, CH_2, NH, O and S, to form a ring having five to eight members provided that such ring is saturated or contains one double bond or is benzo-fused; and wherein Y is one or more a groups selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, alkenyl, alkynyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; or a pharmaceutically acceptable salt thereof;
with the proviso that when each of Ar^1 and Ar^2 is phenyl and each of R^1 and R^2 is hydrido or R^1 and R^2 together form oxo, then X cannot be a linear alkylene chain having four or five carbon atoms so as to form a racemic mixture;
with the further proviso that when Ar^1 is thiophene, then X cannot be oxygen atom or a linear alkylene chain having five carbon atoms; and
with the further proviso that when Ar^1 is para-methylphenyl or para-methoxyphenyl and each of R^1 and R^2 is hydrido and Ar^2 is phenyl, then X cannot be a linear alkylene chain having five carbon atoms,

for preparing a medicament for controlling neuropathological processes and the neurodegenerative consequences thereof in mammals.

18. Use according to Claim 17 wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl, cycloalkyl, hydroxyl, halo and alkoxy, or wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to eight ring carbons; wherein each of Ar^1 and Ar^2 is independently selected from phenyl, thienyl, furanyl, pyridinyl, thiazolyl and naphthyl groups, and wherein any of the foregoing Ar^1 and Ar^2 groups having a substitutable position may be substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, alkenyl, alkynyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein X is selected from CH, CH_2, NH, O and S, to form a ring having five to eight members provided that such ring is saturated or contains one double bond; and wherein Y is a group selected from hydrido, alkyl, halo, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto.

19. Use according to Claim 18 wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl, cycloalkyl, hydroxyl, halo and alkoxy, or wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated cycloalkyl carbocyclic group having three to eight ring carbons; wherein each of Ar^1 and Ar^2 is a group independently selected from phenyl, thienyl, furanyl, pyridinyl, thiazolyl and naphthyl groups, and wherein any of the foregoing Ar^1 and Ar^2 groups may be substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, alkenyl, alkynyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein X is selected from CH or CH_2 to form a ring having five to seven members provided that such ring is saturated or contains one double bond; and wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy, amino, cyano, nitro and mercapto.

20. Use according to Claim 19 wherein the compound is of the formula



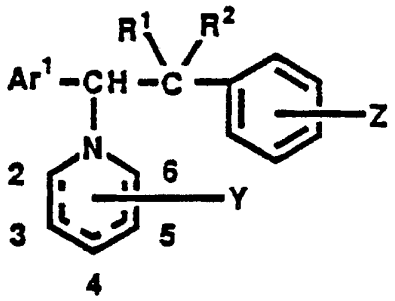
wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl, cycloalkyl, hydroxyl, halo and alkoxy, or wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to seven ring carbons; wherein Ar^1 is a group selected from phenyl, thienyl, furanyl, pyridinyl, thiazolyl and naphthyl groups, and wherein any of the foregoing Ar^1 groups having a substitutable position may be substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy and amino; and wherein Z is one or more groups selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto.

21. Use according to Claim 20 wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl, cycloalkyl, hydroxyl, halo and alkoxy, or wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to seven ring carbons; wherein Ar^1 is selected from phenyl, thienyl, pyridinyl and naphthyl groups, and wherein any of the foregoing Ar^1 groups having a substitutable position may be substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy and amino; and wherein Z is one or more groups selected from hydrido, alkyl, cycloalkyl, halo, hydroxyl, alkoxy and amino.

22. Use according to Claim 21 wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl and hydroxyl, or wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to six ring carbons; wherein Ar^1 is a group selected from phenyl, thienyl, pyridinyl and naphthyl groups, and wherein any of the foregoing Ar^1 groups having one or more substitutable position may be substituted with one or more radicals selected from hydrido, alkyl, halo,

haloalkyl, hydroxyl, alkoxy, amino and nitro; wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy, amino; and wherein Z is one or more groups selected from hydrido, alkyl, halo, hydroxyl and alkoxy.

23. Use according to Claim 19 wherein the compound is of the formula



wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl, cycloalkyl, hydroxyl, halo and alkoxy, or wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to seven ring carbons; wherein Ar^1 is a group selected from phenyl, thienyl, furanyl, pyridinyl, thiazolyl and naphthyl groups, and wherein any of the foregoing Ar^1 groups having a substitutable position is substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy and amino; wherein Z is one or more groups selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; and wherein the broken line within the N-containing ring represents a double bond between any two adjacent carbon atoms involving the 2-, 3-, 4-, 5-and 6-positions of the N-containing ring.

24. Use according to Claim 23 wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl, cycloalkyl, hydroxyl, halo and alkoxy, or wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated carbocyclic group having three to seven ring carbons; wherein Ar^1 is a group selected from phenyl, thienyl, furanyl, pyridinyl, thiazolyl and naphthyl groups, and wherein any of the foregoing groups having one or more substitutable positions may be substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy and amino; wherein Z is one or more groups selected from hydrido, alkyl, cycloalkyl, halo, hydroxyl, alkoxy and amino; and wherein the broken line within the N-containing ring represents a double bond between any two adjacent carbon atoms involving the 3-, 4-, 5-positions of the N-containing ring.

25. Use according to Claim 24 wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl, cycloalkyl, hydroxyl, halo and alkoxy; wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated cycloalkyl having three to seven ring carbons; wherein Ar^1 is selected from phenyl, thienyl, pyridinyl and naphthyl groups, and wherein any of the foregoing groups having a substitutable position is substituted with one or more radicals selected from hydrido, alkyl, cycloalkyl, halo, haloalkyl, hydroxyl, hydroxylalkyl, alkoxy, alkoxyalkyl, amino, cyano, nitro and mercapto; wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy and amino; wherein Z is one or more groups selected from hydrido, alkyl, cycloalkyl, halo, hydroxyl, alkoxy and amino; and wherein the broken line within the N-containing ring represents either a double bond between any two adjacent carbon atoms involving the 3-, 4-, 5-positions of the N-containing ring.

26. Use according to Claim 25 wherein each of R^1 and R^2 is a group independently selected from hydrido, alkyl and hydroxyl; wherein R^1 and R^2 may be taken together to form a saturated or partially unsaturated cycloalkyl having three to six ring carbons; wherein Ar^1 is selected from phenyl, thienyl, pyridinyl and naphthyl groups, and wherein any of the foregoing groups having one or more substitutable positions is substituted with one or more radicals selected from hydrido, alkyl, halo, haloalkyl, hydroxyl, alkoxy, amino and nitro; wherein Y is a group selected from hydrido, alkyl, halo, hydroxyl, alkoxy and amino; wherein Z is one or more groups selected from hydrido, alkyl, halo, hydroxyl and alkoxy; and wherein the broken line within the N-containing ring represents either a double bond between any two adjacent carbon atoms involving the 3-, 4-, 5-positions of the N-containing ring.

27. Use according to Claim 19 wherein said active compound is selected from the group consisting of
(-)-1-(1,2-diphenylethyl)piperidine;
(+)-1-(1,2-diphenylethyl)piperidine;
1-(1,2-diphenylethenyl)piperidine;
(±)-1-[1-phenyl-2-(2-pyridinyl)ethyl]piperidine;
1-[1-phenyl-2-(2-pyridinyl)ethenyl]piperidine;
(±)-1-(1,2-diphenylethyl)-1H-azepine;
(±)-1-(1,2-diphenylbutyl)piperidine;
(±)-1-(1,2-diphenyl-3-methylbutyl)piperidine;
(±)-1-(1,2-diphenylethyl)-4-methylpiperazine;
(±)-1-(1,2-diphenylethyl)morpholine;
(±)-1-[1-(1-phenylcyclopentyl)benzyl]piperidine;
(±)-1-[1,2-di(4-methoxyphenyl)ethyl]piperidine;
(±)-1-[1-(1-phenylcyclohexyl)benzyl]piperidine;
(±)-1-[1-(1-phenylcyclopropyl)benzyl]piperidine;
(±)-1-(1,2-diphenylethyl)-3,5-dimethylpiperidine;
(±)-1-[2,2-dimethyl-2-phenyl-1-(2-thienyl)ethyl]piperidine;
(±)-1-[1-(3-methoxyphenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(4-fluorophenyl)-2-phenylethyl]piperidine;
(±)-1-[2,2-dimethyl-1,2-diphenylethyl)piperidine;
(±)-1-[1-(3-methylphenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(2-furyl)-2-phenylethyl]piperidine;
(±)-1-[1-(2-chlorophenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(2-methoxyphenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(1-naphthyl)-2-phenylethyl]piperidine;
(±)-1-(1,2-diphenylethyl)-1,2,3,6-tetrahydropyridine; and
(±)-1-[2-phenyl-1-(2-thienyl)ethyl]-1,2,3,6-tetrahydropyridine.

28. Use according to Claim 27 wherein said active compound is selected from the group consisting of
(-)-1-(1,2-diphenylethyl)piperidine;
(+)-1-(1,2-diphenylethyl)piperidine;
(±)-1-[1-phenyl-2-(2-pyridinyl)ethyl]piperidine;
(±)-1-(1,2-diphenylethyl)-1H-azepine;
(±)-1-(1,2-diphenylbutyl)piperidine;
(±)-1-(1,2-diphenylethyl)morpholine;
(±)-1-[1-(1-phenylcyclohexyl)benzyl]piperidine;
(±)-1-[1-(1-phenylcyclopropyl)benzyl]piperidine;
(±)-1-[1-(3-methoxyphenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(4-fluorophenyl)-2-phenylethyl]piperidine;
(±)-1-(2,2-dimethyl-1,2-diphenylethyl)piperidine;
(±)-1-[1-(3-methylphenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(2-chlorophenyl)-2-phenylethyl]piperidine; and
(±)-1-[1-(2-methoxyphenyl)-2-phenylethyl]piperidine.

29. Use according to Claim 28 wherein said active compound is selected from the group consisting of
(±)-1-[1-(3-methoxyphenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(4-fluorophenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(3-methylphenyl)-2-phenylethyl]piperidine;
(±)-1-[1-(2-chlorophenyl)-2-phenylethyl]piperidine; and
(±)-1-[1-(2-methoxyphenyl)-2-phenylethyl]piperidine.

30. Use according to Claim 29 wherein said active compound is
(±)-1-[1-(2-chlorophenyl)-2-phenylethyl]piperidine.

31. Use according to Claim 27 wherein said active compound is selected from the group consisting of
(±)-1-(1,2-diphenylethyl)-1,2,3,6-tetrahydropyridine;
and (±)-1-[2-phenyl-1-(2-thienyl)ethyl]-1,2,3,6-tetrahydropyridine.

32. Use according to Claim 31 wherein said active compound is
(±)-1-[2-phenyl-1-(2-thienyl)ethyl]-1,2,3,6-tetrahydropyridine.

33. Use according to Claim 18 for preparing a medicament for treating hypoxia, anoxia or ischemia.

34. Use according to Claim 33 for preparing a medicament for treating ischemia.

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EUROPEAN SEARCH REPORT

Application number

DOCUMENTS CONSIDERED TO BE RELEVANT

EP 89110572.8

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
D,X	GB - A - 1 143 263 (ICI) * Example 6; page 5, table, 1st test compound * --	1,17	C 07 D 295/00 C 07 D 211/70 C 07 D 211/14 C 07 D 333/20 C 07 D 307/36 A 61 K 31/395
X	US - A - 4 617 409 (ELISSANDO et al.) * Column 12, lines 13-20 * --	1-4	
X	DE - A1 - 2 610 433 (DAINIPPON PHARMACEUTICAL) * Experiment G (pages 61,62); claim 11 * --	1,2, 17,18	
X	JP - A - 52-39 686 (DAINIPPON PHARMACEUTICAL) * Reference example 1 (page 901); page 897, formula II * --	1,2	
D,X	THE JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 75, no. 13, 1953 R.V.HEINZELMAN et al. "Compounds containing the pyrrolidine ring. Analogs of sympathomimetic amines" pages 3409-3413 * Table 1, nos. 9,25,26,27 * --	1,2, 17,18	TECHNICAL FIELDS SEARCHED (Int. Cl.4) C 07 D 295/00 C 07 D 211/00 C 07 D 333/00 C 07 D 307/00
D,X	THE JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 72, January - April 1950 L.H.GOODSON et al. "Diphenyl-ethylamines.I.The preparation of tertiary amines by the Grignard reaction" pages 358-362 * Table II, 4th compound " --	1,2	
X	CHEMICAL ABSTRACTS, vol. 51,	1-3,	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
VIENNA	07-09-1989	KÖRBER

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	no. 2, January 25, 1957, Columbus, Ohio, USA LOUIS H.GOODSON et al. "1-(Bicyclic carbocyclic aryl)-2(monocyclic carbocyclic aryl) ethylamines and salts thereof which are agents for producing mild analgesia" Abstract-no. 1300g & U.S. 2,711,428, June 21, 1955 --	17,18	
X	CHEMICAL ABSTRACTS, vol. 100, no. 9, February 27, 1984, Columbus, Ohio, USA GABRIELYAN, S.A. et al. "Synthesis and antiinflammatory activity of substituted alpha-aminoacetophenone hydrochlorides" page 568, Abstract-no. 67 937n & Khim.-Farm. Zh. 1983, 17(10),1201-3 (Russ) --	1,17	TECHNICAL FIELDS SEARCHED (Int. Cl.4)
X	CHEMICAL ABSTRACTS, vol. 106, no. 25, June 22, 1987, Columbus, Ohio, USA CI,XIAHONG LEE "Photoinduced eletrontransfer fragmentation of amino alcohols:stereochemical effects and connectivity between one-and two-electron events" page 391, Abstract-no. 213 192h & J.Am.Chem.Soc. 1987, 109 (8), 2536-8 + Chemical Abstracts, vol.	1,2	

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	106, Formula Index, page 2108F, right column, lines 95,96; page 1959F, middle column, lines 70,71; page 1972F, right column, lines 86-88		
X	CHEMICAL ABSTRACTS, vol. 69, no. 17, October 21, 1968, Columbus, Ohio, USA MUNK, MORTON E. et al. "Conformational equilibria in the 2-amino-1,2-diphenylethanol system. I. Nuclear magnetic resonance studies" page 6224, Abstract-no. 66 765j & J.Org.Chem. 1968, 33(9), 3480-6 (Eng).	1-3	
X	CHEMICAL ABSTRACTS, vol. 84, no. 1, January 5, 1976, Columbus, Ohio, USA G.FLAD et al. "New epoxides" page 402, Abstract-no. 4 746e & Bull.Soc.Chim.Fr. 1975, (5-6,Pt.2), 1347-56 + Chemical Abstracts, Ninth Collective Index, Formulas, page 10 440F, middle column, lines 6-16	1-3	TECHNICAL FIELDS SEARCHED (Int. Cl.4)
X	CHEMICAL ABSTRACTS, vol. 87, no. 7, August 15, 1977, Columbus, Ohio, USA UNO, HITOSHI et al. "1-Substituted-4-(1,2-diphenylethyl)piperazines" page 485, Abstract-no. 53 381c	1,2	

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Application number

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Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
	& Japan. Kokai 77 14,782		
X	CHEMICAL ABSTRACTS, vol. 97, no. 22, November 29, 1982, Columbus, Ohio, USA NAKAMURA, H. et al. "Chemical structure and pharmacological activities of diphenylethyl-piperazine derivatives" page 15, Abstract-no. 192 732n & Adv.Endog.Exog.Opioids, Proc.Int.Narc.Res.Conf., 12th 1981, 399-401 (Eng)	1,2, 17,18	
X	CHEMICAL ABSTRACTS, vol. 99, no. 3, July 18, 1983, Columbus, Ohio, USA C.F.BERNASCONI "Nucleophilic addition to olefins.8. Addition of piperidine, morpholine, and n-butylamine to alpha-cyano-4-nitrostil-bene and alpha-cyano-2,4--dinitrostilbene. Kinetics and equilibria" page 550, Abstract-no. 21 676j & J.Am.Chem.Soc.1983, 105 (13), 4349-59 + Chemical Abstracts, Eleventh Collective Index, Formulas, page 14276F, left column, lines 98,99; page 13527F, left column, lines 11,12	1	TECHNICAL FIELDS SEARCHED (Int. Cl.4)
X	CHEMICAL ABSTRACTS, vol. 108, no. 3, January 18, 1988, Columbus, Ohio, USA	1,2, 17,18	

The present search report has been drawn up for all claims

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	K.NATSUKA "Synthesis and structure-activity relationships of 1-substituted 4--(1,2-diphenylethyl)piperazine derivatives having narcotic agonist and antagonist activity" page 550, Abstract-no. 21 847v & J.Med.Chem.1987, 30(10), 1779-87 + Chemical Abstract 108, Formula Index, page 2128F, right column, lines 46-50 --		
P,X	CHEMICAL ABSTRACTS, vol. 109, no. 5, August 1, 1988, Columbus, Ohio, USA S.HAMANN et al. "Synthesis and stereochemistry of the formation of tertiary ß-fluoro amine by fluorination of amino alcohols with N,N-diethyl-1,1,2-trifluoro 2-chloroethylamine (FAR) and mixture of hydrogen fluoride and pyridine" page 582, Abstract-no. 37 477f & J.Fluorine Chem. 1987, 37 (3), 343-56 + Chemical Abstracts, vol. 109, Formula Index, page 2257F, middle column, lines 18-22 --	1-3	TECHNICAL FIELDS SEARCHED (Int. Cl.4)
D,A	CHEMICAL ABSTRACTS, vol. 68, no. 25, June 17, 1968, Columbus, Ohio, USA RYUICHI KIMURA et al.	1,2, 17,18	

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	"Novel arylalkylamines" page 11026, Abstract-no. 114 428e & Japan. 15,937('67) (Cl. 16 E 32), Sept. 1, Appl. May 31, 1965 ----		
			TECHNICAL FIELDS SEARCHED (Int. Cl.4)

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